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Index of Suspicion

2 3-month-old Boy with Micropenis

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AUTHOR DISCLOSURE Dr Tosur has disclosed no financial relationships relevant to this article. Dr Karaviti has disclosed that her husband is founder and CEO of Vivante Health. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 3-month-old previously healthy boy was referred to Endocrinology for evaluation of a micropenis. Small phallic size was first noted by a pediatrician at his 2-week-old health maintenance visit. He is feeding well, making good wet and stool diapers. There is no history of any episodes concerning for hypoglycemia. There was no problem during the pregnancy, during delivery, or after birth. The mother denied smoking, consuming alcohol, medication use, or diabetes during pregnancy. He was born at 40 weeks of gestation via vaginal delivery. The birthweight was 3,544 g. He is not taking any medications. His development is appropriate for his age. There is no family history of male infertility, genital ambiguity, or sudden infant death syndrome. Physical examination reveals a weight and height between the 5th and 15th percentile, a high-arched palate, and mild low-set ears. Review of his previous growth charts showed that his weight was at the 65th percentile at birth, the 30th percentile at 2 weeks of age, and the 23rd percentile at 2 months of age and his height was at the 88th percentile at 2 weeks of age and the 68th percentile at 2 months of age. His stretched penile length is 2 cm with a breadth of 0.7 cm. The urethral opening is in a normal position. The scrotum is well rugated with hyperpigmentation and bilaterally descended testicles. Further blood work and imaging reveal the diagnosis.

DISCUSSION

He underwent pituitary hormonal screenings, including tests for thyroid function, growth factors, and adrenocorticotrophic hormone stimulation, and all the results were normal. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone were undetectable. Antimüllerian hormone and inhibin B levels were normal. Hence, he was diagnosed as having isolated hypogonadotropic hypogonadism. Magnetic resonance imaging of the brain showed normal anatomy of the pituitary, but the olfactory bulbs were bilaterally absent (Fig 1). Hypogonadotropic hypogonadism and absent olfactory bulbs were consistent with Kallmann syndrome. Genetic testing was ordered. He was started on 25 mg of intramuscular testosterone monthly for 3 months to induce penile growth. Response to the treatment will be assessed after the third injection.

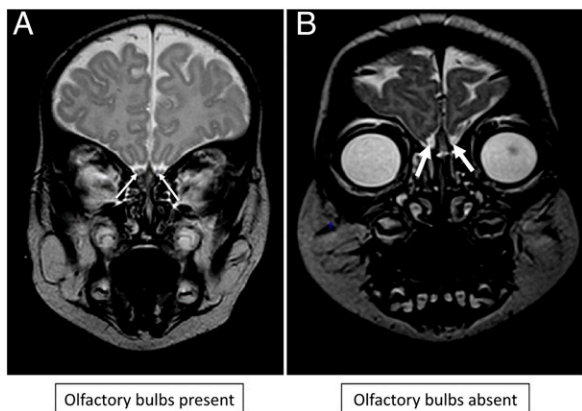


Figure 1. A. A patient with intact olfactory bulbs (thin arrows). B. Our patient with absent olfactory bulbs (thick arrows). (Images courtesy of Dr Jill Hunter.)

Definition and Pathogenesis of Micropenis

Micropenis is defined as a penile length less than 2.5 SD below the mean value for a given age (eg, <2.5 cm for a term baby). Micropenis is mainly caused by deficient fetal testosterone secretion or action. Although hypogonadotropic hypogonadism and primary hypogonadism result in decreased or absent testosterone secretion, the effects of testosterone require binding to a normal androgen receptor, 5 α -reductase activity to produce dihydrotestosterone, and growth hormone to act synergistically with testosterone to induce

penile growth. Thus, a comprehensive evaluation is crucial for diagnosis and management.

The male external genitalia develops from undifferentiated genitalia between 8 and 12 weeks of gestation (Fig 2). Testicular descent and the penile length depend on testosterone production, which is primarily regulated by human chorionic gonadotropin secreted by the placenta until 15 to 20 weeks of gestation, and pituitary gonadotropins (mainly LH) afterward. (1) Also, FSH is important for sertoli cell development and spermatogenesis. (2)

The Condition

Kallmann syndrome is an inherited disorder characterized by hypogonadotropic hypogonadism and anosmia (partial or complete). (3) This is the most common form of gonadotropin deficiency. The molecular pathogenesis includes impairment of olfactory axon development and gonadotropin-releasing hormone neuron migration. (4) It was named after Dr Franz Josef Kallmann, who described the syndrome in 1944. (3) There are at least 17 known genes associated with Kallmann syndrome. (5) Consistent signs and symptoms include micropenis and undescended testicles in boys, infantile ovaries and uterus in girls, and lack of spontaneous puberty and infertility in both sexes. Aplasia or hypoplasia of the olfactory bulbs and a loss of the sense of smell may occur. Very rarely, patients also have unilateral renal

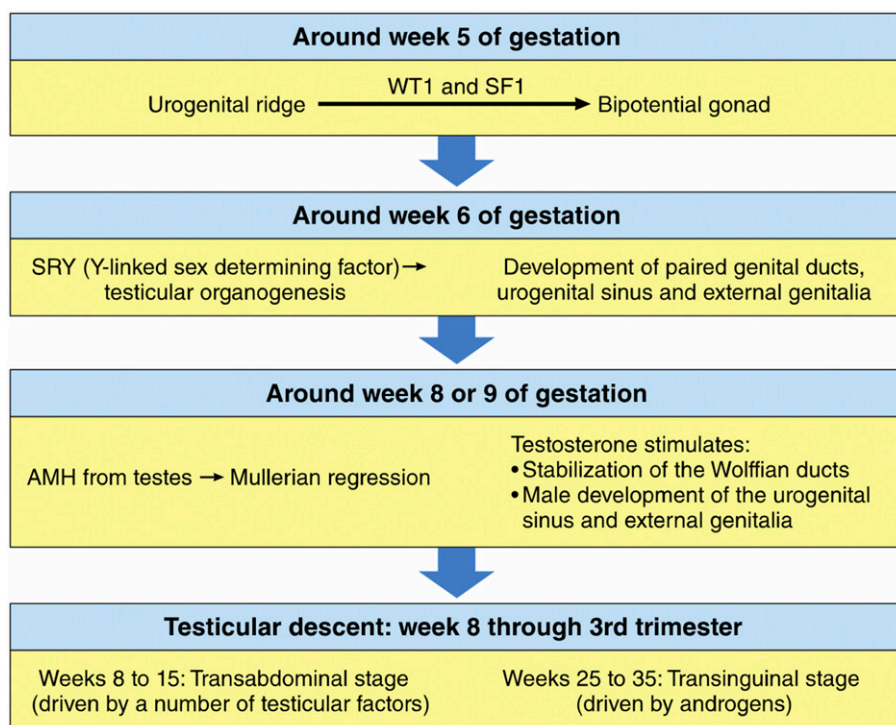


Figure 2. Timing of gonadal determination and differentiation. AMH=antimüllerian hormone.

agenesis, cleft lip and palate, and neurologic problems, including synkinesia (mirror movements), sensorineural deafness, eye movement abnormalities, and mental retardation. (4) Some patients may have color blindness.

Diagnosis

The diagnosis can be made by confirming hypogonadotropic hypogonadism and anosmia. (3) The minipuberty of infancy (up to 6 months in boys and 2–3 years in girls) provides a window of opportunity for confirming hypogonadotropic hypogonadism by demonstrating low sex hormones (testosterone/estradiol) with low LH/FSH. (6) Magnetic resonance imaging of the brain is helpful in identifying aplasia or hypoplasia of the olfactory bulbs and confirming the normal pituitary anatomy. Recognition of smell is a developmental milestone, and odor identification is not reliable in children younger than 6 years. (7) Formal smell testing is the best way to confirm partial or complete anosmia because patients may not be aware. The diagnosis of Kallmann syndrome can also be established in the context of hypogonadotropic hypogonadism and hypoplastic/aplastic olfactory bulbs. A genetic etiology can be identified via genetic testing (hypogonadotropic hypogonadism panel). (8) It is very important to screen patients with hypogonadotropic hypogonadism for other pituitary hormone deficiencies because it can be isolated or a part of hypopituitarism. This can identify a medical emergency in the case of central adrenal insufficiency.

Management

After the diagnosis, patients should be screened for potential associated conditions. Renal ultrasonography, audiology screening, and formal smell testing (if age appropriate) should be considered. (4) Micropenis in males should be managed with a 3-month course of monthly testosterone treatment, (6) preferably within the first 6 months after

birth. Cryptorchidism may require orchiopexy if testicles are not descended by 1 year of age. Once they reach 12 to 13 years of age, both boys and girls require pubertal induction with sex steroids for the development of secondary sexual characteristics, skeletal maturation, and pubertal growth spurt. There are also viable options for fertility in these patients with appropriate treatment regimens, including long-term gonadotropin-releasing hormone administration or subcutaneous gonadotropin injections. (5) Establishing the diagnosis early is key for a patient to develop along with his or her peers. These interventions will enable appropriate penile growth in infancy for males, pubertal induction in adolescence, and fertility in adulthood.

Follow-up

Our patient completed a 3-month course of intramuscular testosterone injections. The stretched penile length was measured as 3.5 cm a month after his completion of testosterone treatment. The genetic testing revealed that he is heterozygous for the c.92-19G>A variant of uncertain significance in the *FGFR1* gene. He was referred to Genetics for genetic counseling and parental genetic testing.

Lessons for the Clinician

- Hypogonadotropic hypogonadism should be considered in cases of micropenis.
- In the context of micropenis, hypopituitarism should be excluded because central adrenal insufficiency might be a medical emergency.
- It is important to determine whether hypogonadotropic hypogonadism is isolated or associated with a genetic defect, structural abnormality, or particular syndrome.

References for this article are at <http://pedsinreview.aappublications.org/content/39/7/363>.

Case 2: 3-month-old Boy with Micropenis

Mustafa Tosur and Lefkothea P. Karaviti

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1 14-month-old Boy with Refusal to Bear Weight

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EDITOR'S NOTE

We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: <https://mc.manuscriptcentral.com/pir>.

AUTHOR DISCLOSURE Drs Struewing and Maul have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 14-month-old boy presents with fever; a swollen, erythematous left leg; and refusal to bear weight. Swelling and bruising were noted in the foot, ankle, and knee after being picked up from child care. He was febrile up to 100.9°F (38.3°C) at home. He has had cough and congestion for the past week with clear rhinorrhea. He was born at 36 weeks' gestation and has a history of chronic otitis media, which resolved with tympanostomy tube placement 2 months ago.

His vital signs are as follows: blood pressure, 105/53 mm Hg; heart rate, 152 beats/min; respiratory rate, 17 breath/min; and temperature, 98.2°F (36.8°C). The boy is sleepy but well-appearing and in no acute distress. He has normal range of motion of all joints, with minimal pain on manipulation of the left ankle. There is erythema over the lateral aspect of the ankle and the dorsum of the foot without fluctuance. He has no pain with passive motion of the hip or knee joints bilaterally. There is drainage from the left ear, suggesting acute otitis media.

Laboratory evaluation demonstrates a white blood cell (WBC) count of 16,200/ μ L (16.2×10^9 /L), a C-reactive protein (CRP) level of 2.7 mg/L (25.71 nmol/L) (reference range, 0–10 mg/L [0–95 nmol/L]), and an erythrocyte sedimentation rate (ESR) of 27 mm/h. Radiographs of the tibia and fibula are normal. Left ankle arthrocentesis reveals bloody fluid with a WBC count of 8,463/ μ L (8.46×10^9 /L). Magnetic resonance imaging of the left lower extremity demonstrated peroneal and anterior tibialis tenosynovitis and subtle myositis of surrounding musculature. He was taken to the operating room, where incision and drainage were performed. Aspirate fluid was collected, and further laboratory testing revealed the diagnosis.

DISCUSSION

The aspirate fluid was sent for routine cultures and Gram-stain, which were negative; a portion of the aspirate was inoculated in blood culture bottles. After incision and drainage by orthopedics, he was treated with vancomycin and ceftriaxone. The aerobic blood culture bottle grew gram-negative rods at 30 hours, and the patient was transitioned to ceftriaxone monotherapy. The boy quickly demonstrated decreased pain and increased range of motion, in addition to normalizing CRP. The gram-negative rod was identified as *Kingella kingae*.

The Pathogen

Kingella kingae is a member of the *Neisseriaceae* family. It is a facultative anaerobic gram-negative coccobacilli, typically presenting in pairs or short chains. (1) *Kingella* species are β -hemolytic and oxidase-positive. It is a non-motile organism that grows on blood and chocolate agar but not on MacConkey agar. (2) *Kingella kingae* is becoming an increasingly common cause of bacteremia and osteo-articular infections in young children aged 6 to 36 months, and it is the most common etiology of joint infections in this age group, due in part to asymptomatic carriage in the oropharynx of children this age. (3) Spread of infection is thought to be due to a concomitant viral infection that damages epithelial cells already colonized by *Kingella*. This can result in a lower respiratory tract infection or invasion into the bloodstream, leading to infection of the skeletal system and other body parts. (2) In one series of 143 consecutive patients diagnosed as having *K kingae* infections, septic arthritis, osteomyelitis, and tenosynovitis accounted for 54.5% of diagnoses, occult bacteremia for 39.2%, lower respiratory tract infection for 3.5%, and ocular infections and bacterial endocarditis each for 1.4%. A review of the epidemiology of *Kingella* infections demonstrates that it most commonly affects the skeletal system, leading to septic arthritis, osteomyelitis, and, in a few reported cases, tenosynovitis. (3) *Kingella kingae* septic arthritis involves the large weightbearing knee, ankle, or hip joints in more than 80% of cases, and *K kingae* causes more than one-quarter of cases of spondylodiscitis in children younger than 5 years. Our patient was a regular attendee at child care, putting him at higher risk for *Kingella* colonization. He had *Kingella* tenosynovitis thought to be due to hematogenous myositis given magnetic resonance imaging findings and then subsequent extension into tendon sheaths.

Diagnosis

A thorough history and physical examination of the patient is crucial in helping to diagnose *K kingae* osteoarticular infections. It is becoming increasingly more common since its discovery, likely due to improvement in microbiologic evaluation of the specimen. *Kingella* is a fastidious organism and infrequently grows on routine culture. However, the probability of isolating *K kingae* is increased by inoculating the specimen in blood culture bottles. (2) In addition, the use of nucleic acid amplification aids in identifying *K kingae* as the etiologic organism.

Additional evaluation for children with this presentation typically includes inflammatory markers such as CRP and ESR, in addition to the complete blood cell count with

differential count. Most children with *Kingella* infections, except those with endocarditis, are well-appearing to moderately ill. (3) They can be afebrile; inflammatory markers such as CRP level, ESR, and WBC count are frequently normal; and joint fluid with a WBC count less than $50,000/\mu\text{L}$ ($<50 \times 10^9/\text{L}$) more than 20% of the time fails to meet the laboratory criteria for septic arthritis. Because of the mild presentation of *K kingae* septic arthritis of the hip, this condition may be misdiagnosed as toxic synovitis, a benign inflammatory condition not requiring antibiotics for management. (3) Therefore, *K kingae* should be considered in children with inability to bear weight not responding to conservative management typically used in toxic synovitis. The history obtained by family, physical examination, and clinical suspicion helps to suggest the diagnosis of *Kingella*.

Management

With appropriate treatment, these children respond well to therapy and return to baseline activity levels. Children generally recover with no sequelae observed as long as the condition is recognized and treated in a timely manner and there is no endocardial involvement. (4) After initiation of appropriate antibiotic coverage, children typically return to weightbearing activity and normal playfulness in a couple of days. *Kingella* species are susceptible to β -lactam antibiotics in addition to macrolides, tetracyclines, and quinolones. (2) Outbreaks of *K kingae* infections are common in child care centers as children of 6 to 36 months are those who are typically colonized. Debate is still occurring regarding whether prophylactic antibiotics for outbreaks should be given. Rifampin has been shown to have good activity against *K kingae* infections, although further research is needed. (2)

Our patient was maintained on ceftriaxone until *K kingae* was identified and his musculoskeletal symptoms improved. The boy was discharged from the hospital on cephalexin to complete a total of 14 days of therapy. At the time of discharge, the patient was tolerating weightbearing activities and his normal state of playfulness.

Lessons for the Clinician

- *Kingella kingae* is a common pathogen identified in osteoarticular infections in children aged 6 to 36 months who attend child care, and it is the most common etiology of joint infections in this age group.
- A high index of suspicion is necessary to make the diagnosis of *K kingae* osteoarticular infections because of their often subtle clinical and laboratory presentation.

- Inoculating synovial fluid into aerobic blood culture bottles increases the likelihood of identifying *Kingella* musculoskeletal infections.
- Nucleic acid amplification assays, when available, can identify *K kingae* in less than 24 hours and decrease the number of bacteriologically unconfirmed pediatric skeletal infections.
- Skeletal infections due to *Kingella* have a fairly benign course with limited sequelae if appropriate treatment is initiated early after recognition of infection.

References for this article are at <http://pedsinreview.aappublications.org/content/39/10/516>.

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6 17-year-old Girl with a Skin Reaction from a Home Remedy

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PRESENTATION

AUTHOR DISCLOSURE Drs Fick, Keshavaram, and McLaughlin have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

A 17-year-old previously healthy girl with no chronic medical conditions presents to the clinic with a rash on her face. Three days before presentation, she awoke with the painful red rash. The day before onset she had pruritus of her chin without any other signs or symptoms and no other changes to the skin per her report. She has no history of eczema or allergies. She uses foundation for makeup and has not changed brands in more than a year. She notes no changes in soap or skin care products. There is no new exposure to detergents, plants, latex, nickel, or jewelry. No family members have similar skin lesions. She has not applied any other creams/lotions to the rash. Over the next 2 days the rash became more erythematous and painful but less pruritic. On presentation to the clinic the rash is erythematous and patchlike, with central ulcerations, well-demarcated borders, and overlying healing bullae along the chin and lower face (Fig). Vitals are all within normal limits. No other rashes are present on physical examination, and there are no other abnormal findings on examination.

On further questioning, a probable diagnosis emerges.



Figure. Clinical images of the chin and face with the described rash on presentation to our clinic, obtained via secure methods.

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/4/218>.

DISCUSSION

The patient admits that she performed an Internet search for home remedies to treat pruritus. She followed a recommendation to apply garlic, ground into a paste, to her face. No other chemicals or components were added to the mixture. She applied the paste in the evening and left it on overnight and awoke with the previously described rash.

This case highlights 2 important lessons: first is the importance of understanding the rare but possible chemical burn–like reaction that can be induced by garlic components and second is the importance of developing open lines of communication and a strong rapport with our adolescent patients to reduce the risk of harmful treatment strategies arising from seemingly benign “natural” home remedies.

The Condition

Garlic is a member of the Alliaceae plant family and has long been used in alternative medicine strategies as well as for culinary purposes. (1)(2) Some studies have shown benefit in adjunctive topical garlic application, when the garlic is extracted and prepared into a solution, for dermatologic conditions such as tinea infection or alopecia areata. (3)(4) Adverse effects of garlic ingestion may include nausea, vomiting, diarrhea, bronchospasm, anaphylaxis, hypoglycemia, and dermatitis, the latter of which can be seen with topical application. (5)(6)(7) The oxidative by-products in garlic have been known in some instances to cause a type IV hypersensitivity contact dermatitis and to involve the epidermis alone. (1)(8) Reports of acute chemical burn reactions are even more rare in the literature, (9)(10)(11)(12)(13)(14) and the cases that are reported often have a history of occlusive dressing application over the garlic paste. (15) In vitro studies have shown that allicin, the oxidative derivative of diallyl disulfide in garlic, is able to induce acantholysis to cause the chemical burn reaction. (16) The present case shows that the less common chemical burn occurrence is possible even without occlusive dressings. Risk of scarring when involvement occurs into the dermis is considered in these cases, and the location and cosmetic/psychological implications are taken into consideration as well.

Management

The concern for dermal involvement and the thin epidermis of the face made for challenging treatment in this patient. She was referred to the burn clinic given the concern for dermal involvement, and there she was prescribed topical antibiotic cream for 6 weeks, consistent with recommended guidelines. She was seen by psychology and occupational therapy while in the burn clinic and has been continuing

with routine occupational therapy visits to prevent contractures. She was referred to dermatology for follow-up care and has been gradually improving. Current problems include postinflammatory hyperpigmentation and scarring from the dermal involvement of her burn, and she is working with dermatology for an optimal long-term cosmetic outcome. Often, if contact dermatitis is a concern, patch testing may be performed to assess for a hypersensitivity reaction. Patch testing was not performed in this patient because the pattern and sequence of her burns in addition to the lack of previous exposure to topical garlic paste was believed, on review of the literature, to be more consistent with acute chemical burn rather than contact dermatitis.

Implications

In addition to informing about a rare adverse effect of topical garlic application, this case also raises awareness of the importance of establishing clear, available, and open lines of communication between physicians and patients. An Internet search performed with the terms *itch of face treatment* returned 493,000 results, and 2 of the top 25 hits suggested garlic paste as one of the treatment options. With the ease of access to information via the Internet and the prevalent use of technology in younger generations, it is critical that practices attempt to grow in parallel with their patients. Clinicians may not be the first or only source of health-care information that our patients use. In addition, the growing number of Internet health resources makes it all the more important that our patients are aware of appropriate and inappropriate resources and the differences between the two. The problem is complicated further in that some remedies, as previously stated, are, in fact, based on supportive data, and trying to delineate when to use a given remedy can become quite challenging for the general public. This is a great opportunity for the pediatrician to provide sound recommendations. The ideal setting is likely one in which patients and parents seek to ask their physician questions regarding symptoms and management rather than an Internet search and before application of compounds that can potentially cause chemical burns. Several resources are available for providers and patients/parents to help facilitate these lines of communication, such as the Natural Medicines Comprehensive Database, the Medicine and the Media initiative from the American Academy of Pediatrics, and others. (17) This case shows a setting where adolescent-specific strategies as well as developing a strong rapport are especially critical.

Lessons for the Clinician

- Garlic can cause a variety of adverse effects, including nausea, vomiting, diarrhea, bronchospasm, anaphylaxis,

and hypoglycemia. In addition, contact dermatitis and chemical burns have been seen in cases of topical garlic application.

- Contact dermatitis is seen more often than chemical burn with garlic application, but it is possible and should be kept in mind with cases of topical garlic application.
- Management of acute chemical burn from garlic application may include topical antibiotic cream and referral to a specialty clinic. Involvement into the dermis, scarring, and associated sequelae should be considered.
- Adequate lines of communication and appropriate use of technology and Internet resources with our patients should be kept in mind as the trend of technology use continues to evolve. Discussing these points and having open communication should questions arise will be important for pediatricians going forward.

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Case 6: 17-year-old Girl with a Skin Reaction from a Home Remedy

Tyler Fick, Ramya Keshavaram and Douglas McLaughlin

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4 18-year-old Young Man with Chest Pressure, Shortness of Breath, Fatigue, and Hyponatremia

Heather Finlay-Morreale, MD*

**Nashaway Pediatrics UMass Memorial Medical Group, Sterling, MA*

AUTHOR DISCLOSURE Dr Finlay-Morreale has disclosed that she was a paid writing fellow for Doximity.com and that stock options were made available at the end of the fellowship. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. Dr. Finlay-Morreale is now Assistant Professor of Pediatrics at University of Massachusetts Medical School, Worcester, MA.

PRESENTATION

An 18-year-old male presents to the emergency department with a 3-day history of chest pressure and shortness of breath. He has a history of pectus excavatum surgery (4 years earlier), juvenile rheumatoid arthritis in remission, and trivial aortic root dilation. As a child he had slightly elevated thyrotropin levels and negative antibodies and briefly took levothyroxine. His heart rate is 91 to 96 beats/min, and his blood pressure (BP) is 100/67 to 110/69 mm Hg. Laboratory results include the following: sodium, 125 mEq/L (125 mmol/L); potassium, 5.4 mEq/L (5.4 mmol/L); chloride, 92 mEq/L (92 mmol/L); carbon dioxide, 24 mEq/L (24 mmol/L); anion gap, 9 mEq/L (9 mmol/L); glucose, 142 mg/dL (7.88 mmol/L); blood urea nitrogen, 33 mg/dL (11.8 mmol/L); creatinine, 0.97 mg/dL (85.75 μ mol/L); glomerular filtration rate, greater than 60 mg/dL; troponin I, less than 0.01 ng/mL (<0.01 μ g/L); brain-type natriuretic peptide, 6 pg/mL (6 ng/L) (reference range, <35 pg/mL [<35 ng/L]); and D-dimer, 0.31 μ g/mL (1.70 nmol/L) (reference range, <0.5 μ g/mL [<2.7 nmol/L]). His electrocardiogram is notable for incomplete right bundle branch block (unchanged from earlier) and ST elevation. Findings from chest radiography are normal. After serious cardiac and pulmonary events are ruled out, he is given a bolus of intravenous normal saline and discharged to follow-up with his primary care doctor who he had not seen for three years. Two days later he presents to his pediatrician with the additional complaint of profound fatigue, which precludes even sitting upright for cardiac auscultation. His heart rate is 65 beats/min, BP is 110/78 mm Hg (similar to previous visits), and oxygen saturation is 100%. A review of his growth chart shows drops in weight and BMI during the past 3 years from the 25th to below the 5th percentile. He denies abdominal or back pain, palpitations, and nausea or vomiting. Echocardiography performed later in an outpatient setting was unrevealing. He receives another bolus of normal saline and is referred to the emergency department, where his BP is 88/33 mm Hg. Shortly after, the diagnosis is determined based on laboratory results, vital signs, and presentation, and definitive treatment is given.

Diagnosis

The patient had hyponatremia, borderline hyperkalemia, hypotension, and profound fatigue. Objectively the patient was pale, but with questioning he revealed

that his friends had noted that he looked more tan than his usual coloration despite it being winter. A diagnosis of primary adrenal insufficiency (PAI) presenting in adrenal crisis was determined. He was immediately resuscitated with normal saline, blood was collected for corticotropin (it was high) and cortisol (it was low), and stress-dose hydrocortisone was promptly given. Once stabilized in the emergency department he was admitted to the hospital for further management.

The Condition

The adrenal gland produces glucocorticoids, mineralocorticoids, and sex hormones. Primary adrenal insufficiency is rare, with approximately 90 to 140 cases per million in developed countries, and an incidence of 4 to 6 new cases per million per year. (1) Globally, tuberculosis and human immunodeficiency virus remain important causes of secondary adrenal failure. Symptoms of adrenal insufficiency include fatigue, weight loss or failure to gain weight or poor growth, postural dizziness, and anorexia. Patients with primary adrenal failure can have hyperpigmentation, but not always (eg, some fair people with red hair who do not tan), and patients with secondary or central adrenal failure do not have hyperpigmentation. During crises, these symptoms progress to severe weakness, abdominal pain, nausea, vomiting, back pain, confusion, and loss of consciousness. Other signs include hypotension, abdominal guarding, and delirium. Laboratory testing will generally show hyponatremia, hyperkalemia, hypoglycemia, hypercalcemia, and possibly elevated renal and hepatic function tests. In children, approximately 70% of new cases of PAI are due to congenital adrenal hyperplasia (CAH), and 45% are due to autoimmune causes. In adults, 85% are autoimmune in nature. (1)(2) In the United States, CAH (specifically, the 21-hydroxylase-deficient, or “salt-wasting” type) is most often identified on the newborn screen. In contrast, primary autoimmune adrenal failure often goes undiagnosed for years and can present with adrenal crisis during times of stress or illness due to glucocorticoid and mineralocorticoid deficiency. A survey of adult patients found that 60% were evaluated by more than 2 physicians before being diagnosed. The same study showed a median of 2 years between onset of symptoms and diagnosis in children, many of whom presented in adrenal crisis. (3) The definitive diagnostic test for adrenal insufficiency is debated. There is a standard-dose corticotropin stimulation test and a low-dose stimulation test. The former consists of administration of 250 μ g of corticotropin being administered (for children \geq 2 years of age; 125 μ g for children 1–2 years, and 15 μ g/kg for

infants). Cortisol levels are then checked at 30 and 60 minutes. A cortisol peak less than 18 μ g/dL (<500 nmol/L) is a positive result. In some instances, it is thought that a more physiologic dose of 1 μ g of corticotropin is more sensitive, and has been advised for cases of secondary or tertiary adrenal insufficiency, recent-onset disease, or mild chronic disease. (1)(4) This patient’s diagnosis was made as above, and stimulation testing was not performed. Once adrenal insufficiency has been identified, its etiology should be sought. In infants, CAH is the primary suspect (72% of cases), (1)(2) and it is identified on newborn screen via an elevated 17-hydroxyprogesterone level. Other congenital causes include adrenal dysgenesis syndromes, corticotropin resistance syndromes, cholesterol synthesis disorders such as Wolman disease and Smith-Lemli-Opitz syndrome, and peroxisomal disorders such as X-linked adrenoleukodystrophy. Due to the possibility of the latter condition, a boy with new-onset adrenal failure should have his very-long-chain fatty acid levels examined. There should be a low threshold for consulting genetics and metabolism for recommendations regarding further diagnostic evaluation. Acquired causes of adrenal insufficiency include hemorrhage, trauma, and destruction by tuberculosis, which can be seen on computed tomographic scans. Positive 21-hydroxylase antibodies are seen in 85% of autoimmune patients. (1)(4)(5) Autoimmune adrenal insufficiency was identified in this young man with positive antibody results. Approximately 50% of the time, other autoimmune conditions are comorbid, including autoimmune polyendocrine syndrome type 1 (involving chronic mucocutaneous candidiasis and hypoparathyroidism) and type 2 (involving autoimmune thyroid disease and type 1 diabetes). Assessing for these conditions is recommended in all patients with primary autoimmune adrenal insufficiency. (4)

Management

Management of adrenal crises includes giving 20 mL/kg of normal saline as needed, followed by isotonic maintenance fluids at 1.5 to 2 times the maintenance rate. Electrolyte abnormalities should be corrected per standard protocol. Immediate intravenous administration of 100 mg (50 mg/m²) of hydrocortisone, followed by 200 mg (50–100 mg/m²) over 24 hours via continuous drip or 6 hourly boluses should be given. Treatment should not be delayed while testing is performed. (1)(4) When treating crises with stress-dose corticosteroids exceeding 50 mg of hydrocortisone per 24 hours (in adults), a mineralocorticoid is not required. (1) One exception is the patient with both newly diagnosed adrenal insufficiency and newly diagnosed hypothyroidism.

In these patients, the hydrocortisone must be given first or a stable patient may be pushed into adrenal crisis. (5) After diagnosis, younger patients take hydrocortisone and fludrocortisone daily, whereas some older patients can forgo fludrocortisone therapy. During times of surgery, illness, significant exercise, or other such stressors, stress dosing is recommended to prevent adrenal crisis. All patients should carry an emergency wallet card and a hydrocortisone injection kit for use in times of an emergency adrenal crisis. (2) There are no published randomized controlled studies on treatment regimens for PAI in children; most data are on CAH. The clinician is cautioned to avoid overtreatment and undertreatment by adjusting dosing for body surface area. (4)

The patient has now been maintained on hydrocortisone and fludrocortisone, and his energy and sense of well-being

have rebounded. He remains thin and has been referred to a nutritionist.

Lessons for the Clinician

- Patients with hyponatremia, fatigue, and poor growth should be evaluated for adrenal failure.
- Adrenal failure can present nonspecifically and can progress to life-threatening adrenal crisis.
- Adrenal crises are medical emergencies and should be promptly treated with hydrocortisone and intravenous fluids.

References for this article are at <http://pedsinreview.aappublications.org/content/39/12/620>.

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**Case 4: 18-year-old Young Man with Chest Pressure, Shortness of Breath,
Fatigue, and Hyponatremia**

Heather Finlay-Morreale
Pediatrics in Review 2018;39;620
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3 A 10-year-old Boy with Saber Shins

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AUTHOR DISCLOSURE Drs Fabie and Misra have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 10-year-old boy is seen for evaluation of short stature and tibial deformity. His medical history is notable for term birth with the following birth parameters: birth weight, 2,460 g (<10th percentile); length, 19.1 in (48.5 cm) (50th–75th percentile); and head circumference, 13 in (33 cm) (25th–50th percentile). His medical history is significant for at least 5 long bone fractures with low-impact trauma as a toddler (Table 1). On physical examination he is thin-appearing, with height at the 4th percentile and weight at the 23rd percentile. Striking anterior bowing of his tibiae (Fig 1) and bowing and decreased forearm supination are observed. There is absence of dental anomalies and scleral discoloration. A skeletal survey demonstrates Wormian bones, diffuse osteopenia, multiple areas of periosteal and cortical thickening, and calcification of the interosseous membrane between the radius and ulna (Fig 2). Specialized testing reveals the diagnosis.

DISCUSSION

Because of the significant tibial bowing, prenatal maternal rapid plasma reagin was reviewed and was noted to be nonreactive. Initial analysis of type I procollagen produced by cultured dermal fibroblasts did not find alterations in the quantity or structure of the type I procollagen molecules made. Sequencing and deletion/duplication analysis of the *COL1A1* and *COL1A2* genes did not reveal any pathogenic changes. Laboratory studies demonstrated an insufficient 25-hydroxyvitamin D level (25 ng/mL [62 nmol/L]; reference range, >30 ng/mL [>75 nmol/L]), an elevated alkaline phosphatase level (491 μ /L [8.2 μ kat/L]; reference range, 100–325 U/L [1.7–5.4 μ kat/L]), normal calcium and phosphorous levels, and elevated spot urine N-terminal telopeptide levels (NTx; 574 nM BCE/mM Cr; reference range, 152–505 nM BCE/mM Cr). Bone mineral density by dual-energy radiograph absorptiometry showed a total-body Z score of –3.4, indicating bone mineral density below the reference range. Molecular genetic testing identified a pathogenic mutation in the *IFITM5* gene, confirming a diagnosis of osteogenesis imperfecta (OI) with calcification in interosseous membranes (OI type V).

TABLE 1. Summary of the Patient's Trauma-Related Injury

| AGE (MO) | MECHANISM OF INJURY | TYPE OF INJURY |
|----------|---------------------------------|---|
| 9 | Fell off bed | Hairline fracture, distal metaphysis, right tibia |
| 12 | Slipped while holding furniture | Fracture, left tibia |
| 26 | Fell while playing | Fracture, right radius and ulna |
| 39 | Fell off bed | Nondisplaced distal fracture, left fibula |
| 39 | Fell from mother's arms | Nondisplaced distal fracture, left ulna |

THE CONDITION

Osteogenesis imperfecta is a group of genetic connective tissue disorders characterized by bone fragility and bone deformity. Traditionally classified into 4 types—OI types I to IV—the identification of new causative genes and expansion of clinical features have led to the addition of new types. Table 2 summarizes the common OI types. Clinically, OI is one of the common disorders with variable expressivity. Each type may present with isolated findings of each or a combination of these clinical features: recurrent fractures, short stature, skeletal abnormalities such as bowing of long

bones, and radiographic features of skeletal dysplasia (Wormian bones, diffuse osteopenia, cortical abnormalities). Laboratory markers of bone turnover (urine NTx, serum alkaline phosphatase) are also elevated. There may be other clinical features, such as blue sclerae, hearing loss, dental abnormalities, and joint laxity, but the presence of these highly depends on the type of OI.

Similar to its clinical presentation, OI is also a genetically heterogeneous disorder. Mutations in the *COL1A1* and *COL1A2* genes account for approximately 85% to 90% of known OI cases. However, during the past decade, genomic technologies have helped revolutionize our understanding of OI, identifying 15 additional genes, to date, that are associated with the disorder.

Osteogenesis imperfecta type V is an autosomal dominant form caused by mutations in the gene *IFITM5*. Patients with this type of OI have moderate or severe bone fragility with progressive calcification of the interosseous membrane. (2) This progressive calcification of the interosseous membrane is unique to this type and may often lead to decreased range of pronation/supination of the forearm and eventual radial head dislocation. Blue sclerae and dentinogenesis imperfecta are typically absent. Wormian bones or accessory skull bones within sutures are nonspecific findings in OI and have been described in OI type V. (3)

DIFFERENTIAL DIAGNOSIS

Our patient presented primarily with anterior bowing of the tibia or “saber shin” deformity. This deformity has been traditionally associated with the treponematoses, particularly late congenital syphilis. However, in developed countries, congenital syphilis is now rarely encountered. Thus, the incidence of this once common infectious disease is now similar to that of rare genetic disorders. As a result, skeletal dysplasias, including OI, various osteochondrodysplasias, and rickets have become a primary



Figure 1. Anterior bowing of the tibiae (saber shins).



Figure 2. Cortical thickening, bony excrescence, and calcification of the interosseous membrane between the right radius and ulna.

consideration in the differential diagnosis of anterior tibial bowing in children. These conditions may be suspected and differentiated based on classic clinical and radiographic findings. Neurofibromatosis type 1 can present with limb deformities but usually is accompanied by café-au-lait spots.

Whereas rickets may also present with similar features of short stature, progressive long bone deformities, diffuse osteopenia, and fractures, the clinical markers of bone turnover and the radiographic features differ. The degree of vitamin D deficiency would usually be more severe and chronic before bony changes are identified. Renal function and/or liver function may be abnormal if

the etiology of rickets is due to chronic liver disease or renal tubular acidosis. Radiographic features of rickets, such as flaring of the anterior aspects of the ribs (rachitic rosary) and widening or splaying of the metaphysis, are not common in OI, and interosseous calcification is usually not seen in rickets. In our case, radiography demonstrated the classic features of cortical thickening and bony excrescence of the interosseous margin of the ulna found in OI type V.

DIAGNOSIS

The diagnosis of OI requires an index of suspicion based on classic clinical and historical features, while accounting for unusual elements of the presentation. Laboratory markers of bone turnover (urine NTx, serum alkaline phosphatase), which are elevated in OI, are also used. Identification of radiographic features will also help guide further molecular genetic testing.

Until the advent of gene sequencing-based methods, the primary test to establish a diagnosis was the electrophoretic analysis of type I procollagen produced by cultured dermal fibroblasts to detect the quantity and structure of type I procollagen. Although this testing could distinguish patients with OI type I, it provided little insight into other forms of OI. Thus, the current first-line strategy to confirm a diagnosis of OI relies on sequence analysis of *COL1A1*, *COL1A2*, and other genes known to cause rarer forms of OI. If the clinical features suggest a specific form of OI, the specific gene testing to confirm the most likely diagnosis is performed. For nonspecific or atypical presentations, all genes can be sequenced concurrently.

MANAGEMENT

The goal of therapy for patients with OI is to maximize their quality of life by decreasing pain and disability while improving mobility and function. Like other forms of OI, the mainstay of treatment for individuals with OI type V include physiotherapy, rehabilitation, and, if necessary, orthopedic intervention. Health supervision considerations for OI were outlined by Starr et al in 2010. (4)

Children with OI type V, as in some forms of OI, may also benefit from cyclic intravenous bisphosphonates to improve bone density and reduce symptoms of osteoporosis. Effect on functional parameters in children, such as improved energy, decreased bone pain, and increased ambulation, are also seen with treatment. Treatment is

TABLE 2. OI Nomenclature with Causative Genes and Clinical Presentation (1)(2)

| OI SYNDROME NAME | TYPE | GENES | FEATURES |
|---|------|--|--|
| Nondeforming with blue sclerae | I | AD: <i>COL1A1</i> , <i>COL1A2</i> | Bone fragility with fractures, blue sclerae, conductive hearing loss |
| Perinatally lethal | II | AD: <i>COL1A1</i> , <i>COL1A2</i> AR: <i>CRTAP</i> , <i>LEPRE1</i> , <i>PPIB</i> | Multiple, severe fractures involving ribs, long bones leading to deformed and crumpled bones; deficiency of ossification of facial and skull bones |
| Progressively deforming | III | AD: <i>COL1A1</i> , <i>COL1A2</i> AR: <i>BMP1</i> , <i>CRTAP</i> , <i>FKBP10</i> , <i>LEPRE1</i> , <i>PLOD2</i> , <i>PPIB</i> , <i>SERPINF1</i> , <i>SERPINH1</i> , <i>TMEM38B</i> , <i>WNT1</i> , <i>CREB3L1</i> | Bone fragility with multiple fractures, short stature, progressive kyphoscoliosis, angulation deformities of long bones, "popcorn" appearance of metaphyses, platyspondyly |
| Common variable OI with normal sclerae | IV | AD: <i>COL1A1</i> , <i>COL1A2</i> , <i>WNT1</i> AR: <i>CRTAP</i> , <i>PPIB</i> , <i>SP7</i> XL: <i>PLS3</i> | Fractures, osteoporosis, variable degree of long bone deformity; high risk for basilar impression |
| OI with calcification in interosseous membranes | V | AD: <i>IFITM5</i> | Calcification of forearm interosseous membrane, radial head dislocation, hyperplastic callus formation |

AD=autosomal dominant, AR=autosomal recessive, OI=osteogenesis imperfecta; XL=X-linked.

given intravenously, and complications that have been described include flulike symptoms ("acute phase reactions") with the first infusion and transient hypocalcemia. (1)(5)

Lessons for the Clinician

- Anterior bowing of the tibia may be seen in an extensive number of diseases from infectious etiologies to genetic syndromes.

- Osteogenesis imperfecta (OI) is highly variable in its clinical presentation, and molecular testing via sequencing of genes associated with OI is necessary to obtain a definite diagnosis.
- Intravenous bisphosphonate treatment in OI has been shown to improve bone density and decrease disability in children with OI.

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3 A 17-year-old Boy with 6 Weeks of Left Neck Swelling

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PRESENTATION

A 17-year-old boy with a history of autism spectrum disorder, small lymphatic malformation on the scalp, and scoliosis presents to the emergency department with a 6-week history of left lower neck swelling. He was initially evaluated by his primary care physician and completed a 10-day course of clindamycin for presumed lymphangitis. The swelling initially improved, but within a few days of stopping clindamycin, the swelling worsened again. He was restarted on clindamycin, and given the recurrence of symptoms, a computed tomographic scan of the neck and chest was obtained (Fig 1). Findings showed a large, nonenhancing, low-density mass extending from the left neck down into the superior mediastinum and left upper thorax with mild rightward displacement of cervical and mediastinal structures and encasement of the left subclavian artery. No airway compression or narrowing was noted. He was transferred to our institution for further evaluation with concern for a possible neoplastic process.

In the emergency department he is afebrile, with a heart rate of 90 beats/min, a respiratory rate of 18 breaths/min, and blood pressure of 115/73 mm Hg. Physical examination shows an alert and oriented patient in no respiratory distress. There is notable swelling over the left anterior neck immediately above the clavicle measuring 3 × 4 cm. It is fixed, hard, and nontender to the touch. There is no overlying erythema or warmth. No cervical or axillary lymphadenopathy is noted.



Figure 1. Chest computed tomographic scan showing the craniocaudal length (13.4 cm) of the plexiform neurofibroma.

AUTHOR DISCLOSURE Drs Almaghraby, Chason, and Banigan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 2. Chest magnetic resonance image in the transverse view showing the width (5.3 cm) and depth (5.9 cm) of the plexiform neurofibroma.

Skin examination reveals multiple café-au-lait spots on the right upper back (15 × 10 mm), left lower abdomen (30 × 15 mm), and right anterior neck (10 × 5 mm). A soft mobile nodule is palpated on the right parieto-occipital scalp that the parents refer to as his small lymphatic malformation. No axial or inguinal freckling is noted. Eye examination shows multiple slightly raised, brown, hyperpigmented lesions on both irides.

Results of his complete blood cell count, electrolytes, glucose, amylase, lipase, liver enzymes, coagulation studies, uric acid, and lactate dehydrogenase were all normal. Inflammatory markers, including erythrocyte sedimentation rate and C-reactive protein, were also within normal limits. Peripheral blood smear showed no abnormalities. Further imaging and genetic testing revealed the diagnosis.

DISCUSSION

Magnetic resonance imaging of the neck and chest was performed and showed a large multiloculated solid mass

with restricted diffusion and signal characteristics extending from the C4-C7 neural foramina down into the superior mediastinum partially encasing the aortic arch (Fig 2). Findings seemed to be most consistent with a large plexiform neurofibroma. Additional T2 hyperintense foci were noted in the anterior chest wall and the medial aspect of bilateral arms consistent with small neurofibromas. A biopsy of the mass was subsequently performed by interventional radiology and is consistent with intraneural neurofibromas (Figs 3 and 4). An ophthalmology evaluation confirmed the presence of Lisch nodules. Given the findings of café-au-lait spots, Lisch nodules, and a plexiform neurofibroma, he met the diagnostic criteria for neurofibromatosis type 1 (NF1). Genetic testing revealed a pathogenic mutation in the *NF1* gene designated c.5923delA (p. Ile1975TyrfsTer18). More specifically, there is a deletion of an “A” nucleotide in the 5923rd position of the gene resulting in a frameshift and the creation of a premature stop codon with truncation of the protein product, which confirms the diagnosis. The patient’s mother and sibling tested negative

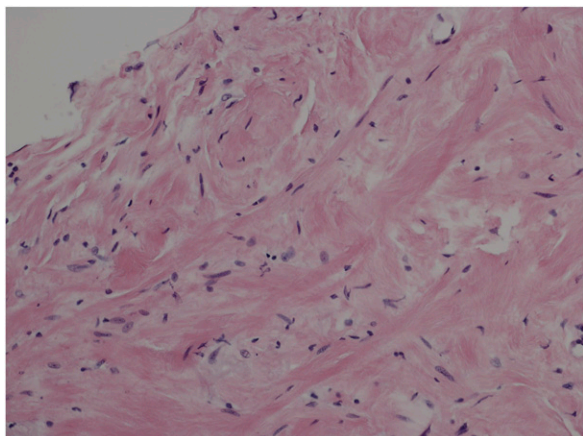


Figure 3. Microscopic examination with hematoxylin and eosin stain showing minimally cellular sample with intertwining fiber bands not arranged in parallel form.

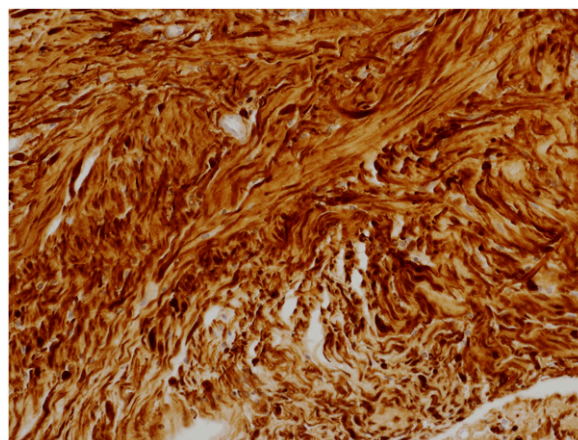


Figure 4. Microscopic examination with S100 stain showing a fascicular appearance and a rare ganglion cell.

for NF1. Because the plexiform neurofibroma encases numerous vascular structures, including the aortic arch and the left subclavian and vertebral arteries, the mass was deemed inoperable. Given the size of the mass with increased risk of malignant transformation, he was started on a clinical trial with selumetinib (MEK inhibitor).

Plexiform neurofibromas are benign, slow-growing tumors that mostly start developing at puberty. They can be seen in 20% to 50% of patients with NF1. Their size can increase by 20% per year. (1) Selumetinib is an oral selective inhibitor of MEK 1 and 2 that was shown in clinical trials to induce noticeable tumor regression. It is usually administered twice a day in a 28-day cycle. The maximum response of selumetinib seems to be more pronounced after 20 cycles by decreasing the tumor volume by up to 31%. (2) In our patient, selumetinib induced a decrease in the tumor volume by 15% after 7 cycles, but, unfortunately, it had to be discontinued due to severe pancreatitis.

Lessons for the Clinician

- If 6 or more café-au-lait spots (measuring ≥ 0.5 cm in a child or ≥ 1.5 cm in a postpubertal adolescent) are identified on examination, clinicians must be diligent and look for a second defining feature that may confirm the diagnosis of neurofibromatosis type 1.
- Plexiform neurofibromas can grow internally and not be recognized until they cause symptomatic impingement on a surrounding structure.
- Patients with plexiform neurofibromas that are deemed inoperable and at risk for malignant transformation are now being enrolled in clinical trials with investigational drugs, including selumetinib (MEK inhibitor).

References for this article are at <http://pedsinreview.aappublications.org/content/39/9/470>.



Index of Suspicion

4

A Patterned Acute Skin Lesion on a Leg of a 17-month-old Boy

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AUTHOR DISCLOSURE Drs Kellogg, Northrop, and Browning have disclosed no financial relationships relevant to this article. Dr Northrop's current affiliation is Wake Forest Baptist Health, Winston-Salem, NC. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 17-month-old previously healthy boy presents to the emergency department with an unexplained skin lesion on his right leg. The mother reports seeing the lesion a few hours ago when the child returned home from a 2-day visit with his father. She says the father noted the mark 2 days earlier, and asked her if the child was allergic to socks. The parents have been separated since the child's birth and share custody of their son. The treating physician notes a "bright red lesion" on the right leg posteriorly that is "sharply marginated," photographs the lesion (Fig), and documents the lesion as suspicious for "nonaccidental trauma with an electric cord." A report is made to Child Protective Services. However, the child does not undergo evaluation for abuse.

A child abuse specialist sees the child 3 days later. The mother indicates that the child had stated that his father hit him. The mother states that her son at 2 months of age had a similar, yet more proximal mark on the same leg, and she produces photographs taken at the time that her son's previous lesion appeared. A physician examined the infant about 1 week after the first lesion appeared, but the physician was unable to determine a cause. The lesion resolved spontaneously over a few weeks.



Figure. An erythematous, slightly raised lesion is seen on the posterior aspect of the right leg.

The child has no previous hospitalizations but is allergic and/or sensitive to several substances, including turkey, milk, gluten, human milk, soaps, and detergents. He is currently taking amoxicillin and a nonprescription cough medicine for bronchitis.

On examination by the child abuse specialist, the lesion appears unchanged compared with photographs taken 3 days previously; the lesion is erythematous, slightly raised

to palpation, with small vertical hatch marks noted medially, and is seen on the posterior aspect of right leg (Fig). The remainder of his examination findings are completely normal.

The Case Discussion and Suggested Readings appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/3/145>.

DISCUSSION

Additional information was obtained from the father by telephone after the clinic visit. During the first incident at age 2 months, the father confirmed that the infant was wearing an infant garment with pant legs. The mother was caring for the infant when the first lesion was observed. The second and current skin lesion was noted by the father 1 to 2 hours after the patient wore new unwashed toddler-sized socks made of polyester, spandex, rubber, and nylon. The child abuse specialist referred the child to a dermatologist 5 days after the second lesion appeared. A biopsy of the lesion was nonspecific, and only lymphocytes were visualized, with no evidence of thermal injury or allergic contact dermatitis. Three weeks later, the child developed another similar red curvilinear lesion on the anterior part of the right leg 1 to 2 hours after wearing washed cotton blend socks.

THE CONDITION

Infantile garment bands, or sock line bands, are considered a rare condition, with approximately 20 cases, mostly involving infants, described in the literature. Previous case reports have indicated tight garment bands/elastics as the most likely cause for these lesions, although some reports have mentioned factors such as dermal inflammation and panniculitis, dermatographism, and activation of mast cells. The band lines described are typically continuous, partially circumferential, and involve the posterior region of legs, although some bands occurred on the thighs and wrists. Other reported characteristics of sock line bands included blistering focal desquamation, hyperpigmentation, and bilaterality. Comorbid conditions were not commonly present, although some children had eczema. None of the publications have described recurrent sock line bands. The bands may occur from pressure-induced irritation of the skin. The tightness causes constriction of the epidermis, and this leads to irritation and inflammation, resulting in erythema. Postinflammatory hyperpigmentation occurs in some cases and can persist for months or years.

It is surprising that the condition is considered rare. We speculate that, in reality, it is not a rare condition but only rarely reported in the medical literature. Imprints from garment bands may present as bright erythematous lines and can persist for months or years.

Based on clinical presentation, examination findings, and biopsy results, the underlying mechanism for the garment bands in this child was undetermined. Although others have reported mast cell degranulation as a possible mechanism, only lymphocytes and no mast cells were seen on biopsy of

our patient's lesions. Of interest, related to this case is that all lines occurred on the right calf: 2 were posterior and 1 anterior. In addition, none of the lines were completely circumferential, as may be expected with constriction occurring circumferentially.

DIFFERENTIAL DIAGNOSIS

Patterned injuries, particularly in infants, are highly concerning for physical abuse. When skin lesions are unexplained, the concern for abuse is typically higher, especially if the infant is not yet mobile. Accidental injuries in mobile children tend to be nonpatterned and occur overlying anterior bony prominences.

Dermatologic conditions that may produce distinct patterns that mimic traumatic injuries include phytophotodermatitis and chemical burns. Other conditions that are reported to resemble garment line bands are amniotic bands, acquired raised bands of infancy, pigmentary mosaicism, dermal melanocytosis, linear epidermal nevus, and incontinentia pigmenta. Although acquired raised bands of infancy are associated with swelling and discoloration at the line of elasticized sock tops, infants with this condition typically have dermatographism from birth and recurrent episodes of cutaneous whealing; some also have congenital constriction bands. In contrast to garment bands, acquired raised bands of infancy become progressively palpable after the redness fades and biopsy shows an infiltrate of adipocytes along capillaries in the upper dermis. Raised bands of infancy are more often skin colored, asymmetrical, and persistent; can be progressive; and are typically associated with limb defects. A similar condition, congenital curvilinear palpable hyperpigmentation, has been described but is thought by some to be sock line bands.

In this case, the lesion did not change in appearance over 4 days but resolved within a few weeks. A thin line of hyperpigmentation persisted for 3 months after the first episode of garment band but was not seen after the 2 subsequent lesions.

MANAGEMENT AND PROGNOSIS

There is no specific treatment for garment bands. Most lesions resolve without any permanent skin scarring or pigmentary abnormalities.

Lessons for the Clinician

- Although patterned lesions resembling injuries in young children and infants are generally concerning for abuse, the clinician may consider other nontraumatic causes for such lesions

- Photodocumentation over time can be useful in differentiating traumatic and nontraumatic causes of skin lesions.

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Case 4: A Patterned Acute Skin Lesion on a Leg of a 17-month-old Boy

Nancy Kellogg, Sarah Northrop and John Browning

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Index of Suspicion

5

A Very Tall 7-year-old Boy with Medulloblastoma

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AUTHOR DISCLOSURE Dr Rossfeld has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 7-year-old boy diagnosed 3 months earlier as having medulloblastoma and actively receiving chemotherapy is admitted to the oncology service for *Aspergillus* surgical site infection after tumor resection. He undergoes surgical debridement and is started on appropriate intravenous antifungal treatment, with a favorable clinical response. Although afebrile and clinically convalescing, lower extremity blood pressures (BPs) measured via automated electronic sphygmomanometer are persistently elevated (125–150/65–90 mm Hg), prompting a nephrology consultation.

Physical examination is notable for an irritable boy who is large for his age (height, 59.8 in [152 cm] [100th percentile]; and weight, 125.2 lb [56.8 kg] [100th percentile]), a manual upper extremity BP of 120/84 mm Hg, alopecia, and normal cardiopulmonary examination without peripheral edema.

Results of initial evaluation for causes of secondary hypertension, including urinalysis, serum chemistry/electrolytes/glucose, complete blood cell count, plasma renin activity, renal ultrasound, and echocardiogram, are normal. Additional history and evaluation reveal the diagnosis.

The Case Discussion, References, and Suggested Readings appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/1/41>.

DISCUSSION

Attempting to reconcile BP readings by age, sex, and height, (1) it was realized that the patient's height exceeded the 95th percentile for age by 8.3 in (21 cm). His parents denied any growth spurt and reported that he had "always been heavy and tall." They had, however, noticed axillary and pubic hair as well as body odor for the preceding 5 months. His pediatrician was contacted, and a 1-year height velocity of 6.3 in (16 cm) was confirmed (mean for boys in the same age range is 2.2 in [5.5 cm]). Further evaluation was notable for 6-mL testes (Tanner stage II), bone age of 13 years (+6.6 SD), and, on early-morning measurement, elevated levels of total testosterone (22 ng/dL [0.76 nmol/L]; reference range for age, <2.5–10 ng/dL [<0.09–0.35 nmol/L]) and luteinizing hormone (LH) (0.63 mIU/mL [0.63 IU/L]; reference range for age, <0.2 mIU/mL [<0.2 IU/L]), whereas the follicle-stimulating hormone (FSH) level (0.87 mIU/mL [0.87 IU/L]) was within the reference range for age (<0.2–2.2 mIU/mL [<0.2–2.2 IU/L]). Brain magnetic resonance imaging demonstrated a normal pituitary gland, and the thyrotropin concentration was within the reference range. He was diagnosed as having central precocious puberty (CPP).

Central precocious puberty has been described in association with posterior fossa tumors. Despite a normal pituitary gland by magnetic resonance imaging, the proposed mechanism for CPP in this context is mass effect from the space-occupying lesion causing release of gonadotropin-releasing hormone (GnRH). For the one other case of CPP described specifically in association with medulloblastoma, (2) gonadotropins returned to prepubertal levels after tumor resection and chemotherapy/radiotherapy.

Having previously undergone tumor resection, this boy was administered leuprolide, which suppressed further

pubertal changes. At follow-up 9 months after diagnosis of CPP, levels of LH (0.3 mIU/mL [0.3 IU/L]; reference range, 1.2–8.6 mIU/mL [1.2–8.6 IU/L]), FSH (1.3 mIU/mL [1.3 IU/L]; reference range, 1.3–19.3 mIU/mL [1.3–19.3 IU/L]), and testosterone (<0.1 ng/dL [<0.01 nmol/L]; reference range, 0.03–0.3 ng/dL [0–0.01 nmol/L]) were suppressed, and pituitary gland evaluation revealed thyrotropin, insulinlike growth factor-1, and insulinlike growth factor-binding protein 3 within their respective reference ranges. He has been taking amlodipine, with adequate BP control.

The Condition

Puberty is a nonspecific term that describes sexual maturation during adolescence. Puberty encompasses gonadarche—the maturation of the hypothalamic-pituitary-gonadal axis—and adrenarche—an independent but contemporaneous increase in adrenal production of androgens. The physiology of these processes is incompletely understood, but pulsatile GnRH is known to be imperative for gonadarche.

Our understanding of normally developing secondary sexual characteristics—as elucidated by Marshall and Tanner, (3)(4) the US Health Examination Survey, (5)(6) and more recently the Pediatric Research in Office Settings Network (7)(8) and NHANES III (9) data—suggests that the mean age at onset is 10.5 years for girls and 11.5 years for boys and follows an approximately normal distribution, with the SD being 1 year. A trend has been observed toward earlier onset for children of African American ethnicity and for girls compared with boys, but there has been no consensus to accept pubertal onset less than 2.5 SD below the mean age as normal. Puberty is, therefore, precocious if occurring before age 8 years in girls and 9 years in boys. In addition to early thelarche and pubarche, a height velocity consistently

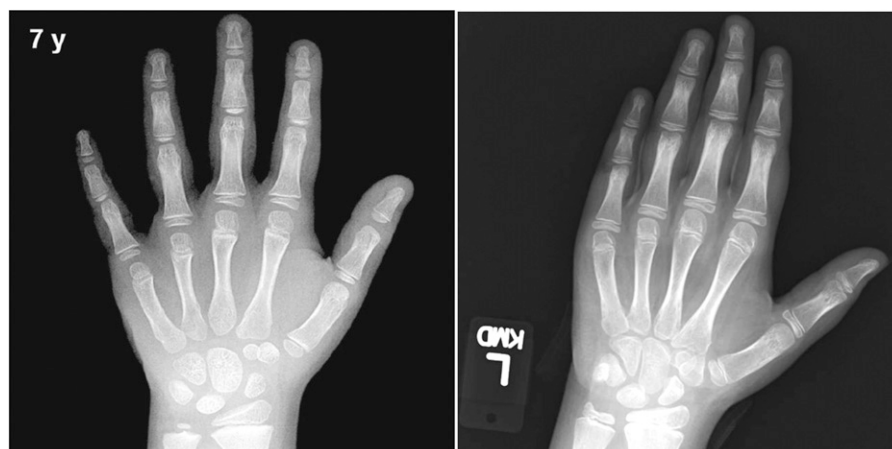


Figure. Bone age. Comparison with the reference image (left) reveals the 7-year-old patient (right) to have advanced bone age. Radiologic impression was bone age of 13 years (+6.6 SD). Reference image reproduced with permission from Gilsanz V, Ratib O. *Hand Bone Age: A Digital Atlas of Skeletal Maturity*. Heidelberg, Germany: Springer-Verlag Berlin; 2005.

above the 75th percentile warrants evaluation for precocious puberty.

The prevalence of precocious puberty is uncertain. Following the logic for a normal distribution, one would expect 2.5% of children to be affected. Available data, however, are discordant. A Danish registry-based study (10) reported the prevalence of a precocious puberty diagnosis of 0.2% for girls and less than 0.05% for boys. Meanwhile, a cross-sectional study of more than 17,000 girls across more than 25 states and Puerto Rico (7) reported stage 2 sexual maturation for 7-year-old girls at 6.7% and 27.2% prevalence for white and African American girls, respectively. Suggesting a trend toward earlier onset of puberty and racial differences, this study was limited by less than 10% of the study population being African American and visual inspection rather than palpation of breast tissue.

Differential Diagnosis

The differential diagnosis for suspected precocious puberty includes nonprogressive pubertal variants (ie, premature adrenarche, premature thelarche), CPP, and peripheral precocious puberty (PPP).

Nonprogressive variants of puberty may have isolated physical examination findings suggesting precocity and require serial monitoring to ensure continued absence of other secondary sex characteristics as well as normal bone age and height velocity.

Central precocious puberty represents activation of the hypothalamic-pituitary-gonadal axis and presents with the expected pubertal sequence, consistent with the child's biological sex, at an early age. Idiopathic causes predominate, but certain genetic causes are being elucidated. (11)(12) Other cases relate to an intracranial lesion or past cranial irradiation. Laboratory testing demonstrates pubertal LH and FSH levels that are suppressible by GnRH agonists.

Peripheral precocious puberty, in contrast, is independent of an active physiologic hormonal axis and manifests as a result of inappropriate exposure to sex hormones. This may occur from excess gonadal or adrenal sex hormone production, exposure to exogenous steroids, or, more rarely, germ cell tumors and may cause symptoms either consistent with or contrary to (eg, virilization of females) biological sex. In PPP, LH and FSH levels are suppressed and do not respond to stimulation by GnRH.

Management

The underlying etiology of precocious puberty drives its treatment. Primary causes, such as intracranial lesions or germ cell tumors, require targeted specialty care. For idiopathic causes of CPP, the decision to treat with GnRH agonists is based on the individualized need for delaying puberty, with attention to

psychosocial issues and preservation of adult height. Treating PPP requires medical therapy to limit the production of (eg, finasteride, anastrozole) and/or response to (eg, spiro-nolactone, tamoxifen, bicalutamide) excess sex hormones.

Lessons for the Clinician

- Hypertension now affects almost 5% of children, and secondary causes are present in 70% to 85% of affected patients younger than 12 years.
- Puberty is precocious if occurring before age 8 years in girls and 9 years in boys.
- In addition to early thelarche and pubarche, a height velocity consistently higher than the 75th percentile warrants evaluation for precocious puberty.

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6

Abdominal Distention and Constipation in a 70-day-old Female Infant

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AUTHOR DISCLOSURE Drs Lancaster, Lear, Brant, Riedel, and Minardi have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 70-day-old female infant presents to the emergency department (ED) with a 1-month history of abdominal distention and constipation. The patient was born at term via vaginal delivery. She is formula fed with a cow milk protein formula and routinely consumes 4 oz every 4 hours. She passed meconium within 24 hours after birth. However, since that time she has not stoolled regularly, and her parents have administered daily diluted fruit juices and enemas every other day to promote defecation. Despite these interventions, her abdomen has become more distended, and the parents report that her constipation continues.

In the ED her vital signs are temperature 98.6°F (37.0°C), blood pressure 111/62 mm Hg, pulse 137 beats/min, respiratory rate 22 breaths/min, and oxygen saturation 100% on room air. Her examination shows a well-appearing baby in no apparent distress. Her cardiopulmonary examination findings are normal. Extremity examination shows capillary refill within 2 seconds, and there is no appreciable edema. Peripheral pulses are strong. The patient's abdomen is distended but nontender and without any cutaneous findings suggesting portal hypertension. Bedside abdominal ultrasonography performed by the ED physician demonstrates ascites without any organomegaly (Fig 1). She is admitted to the pediatric service at that time.

Results of laboratory studies are largely normal (aspartate aminotransferase, alanine aminotransferase, albumin, electrolyte panel, and lipase) except for peripheral eosinophilia noted on the complete blood cell count (white blood cell count, 10,500/ μ L [10.5×10^9 /L]; eosinophils, 15%; absolute eosinophil count, 1.5×10^9 /L). The total serum immunoglobulin E (IgE) level is normal at 3.36 mg/L. An echocardiogram is obtained that reveals normal cardiac function and anatomy. Consultative ultrasonography is completed, again demonstrating uncomplicated ascites. The patient is sent to the interventional radiology service for image-guided sampling of the ascitic fluid. Twenty milliliters of milky white fluid is removed

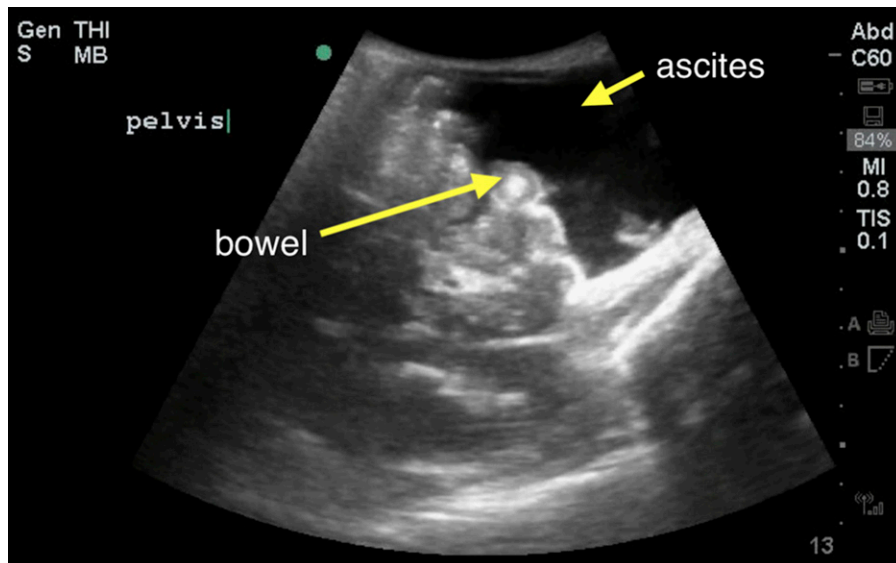


Figure 1. Ascites is seen in the pelvis surrounding multiple intestinal loops.

from the abdomen and sent to the laboratory, which verifies a triglyceride-rich fluid consistent with chylous ascites (CA) (fluid triglyceride level, 3,509 mg/dL [40 mmol/L]).

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/3/148>.

DISCUSSION

Due to the findings of CA and peripheral eosinophilia, milk protein allergy was suspected, and the patient was changed to an elemental formula. Despite changing formula, the patient continued to have worsening eosinophilia (25%). She was taken to the endoscopy suite, where an esophago-gastroduodenoscopy was performed showing patchy gastric and duodenal erythema, and a flexible sigmoidoscopy was performed and had normal findings. Mucosal biopsies of samples taken from this tissue revealed eosinophilic infiltration of the lamina propria of the stomach and duodenum, focally in numbers as great as 25 per high-power field, including prominent eosinophil degranulation (Fig 2). The villous architecture of the duodenum was normal. The rectosigmoid biopsy showed rare eosinophilic cryptitis and occasional stromal eosinophils. In the clinical context, the pathology results were strongly supportive of eosinophilic gastroenteritis (EG), likely due to milk protein allergy.

Per Cárdenas and Chopra (1), “Chylous ascites is the accumulation of a milk-like peritoneal fluid rich in triglycerides, due to the presence of thoracic or intestinal lymph in the abdominal cavity. It develops when there is disruption of the lymphatic system due to traumatic injury or obstruction (from benign or malignant causes).” In this patient there is an absence of a major lymphatic malformation, trauma, or recent surgery. Therefore, the most likely explanation for the development of CA is lymphangiectasia due to inflammation caused by EG. Lymphangiectasia can be patchy and challenging to confirm on endoscopic biopsy so its absence in our patient’s duodenal biopsy samples does not rule it out. (2) As a result of our patient’s subsequent

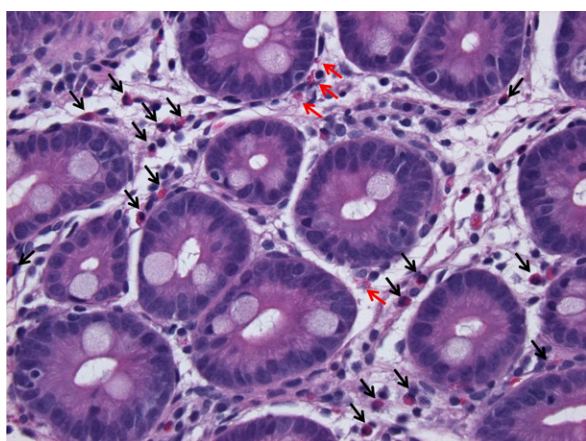


Figure 2. Mucosal biopsy showing eosinophilic infiltration of the lamina propria of the stomach and duodenum (black arrows), focally in numbers as great as 25 per high-power field, including prominent eosinophil degranulation (red arrows).

clinical course, we believe that her CA is due to secondary, and not primary, lymphangiectasia.

THE CONDITION

Eosinophilic gastroenteritis is a term used to describe one of the eosinophilic gastrointestinal disorders, which also include eosinophilic esophagitis, gastritis, enteritis, and colitis. Eosinophilic gastroenteritis is a rare inflammatory disease in children that manifests by infiltration of eosinophils in the gastric and small-bowel mucosa without other known cause of eosinophilia. Although there are limited data on the prevalence of EG, it is estimated to affect 22 to 28 per 100,000 people in the United States. (3)

The pathogenesis of EG is poorly understood, but it seems that there is likely an allergic component to the disease because elemental or elimination diets often improve symptoms, according to several reports. (4) In addition, most children with EG also have an increased serum IgE level. In patients with allergic EG, a population of interleukin 5-expressing food allergen-specific T-helper 2 (Th2) cells has been identified. (5) It is theorized that food exposure activates these Th2 cells, which then release chemokines (specifically, eotaxins), which lead to recruitment of eosinophils to the gut. (6) Once present, eosinophils induce local inflammatory change by 2 mechanisms. First, eosinophils mediate a pro-inflammatory effect through the release of cytokines, chemokines, and lipid mediators. Second, eosinophils induce tissue damage directly through the release of toxic mediators such as major basic protein and eosinophilic cationic protein. (7)(8)

The clinical presentation of EG varies, depending on the location in the gastrointestinal tract and the extent of eosinophilic infiltration in the layers of the affected region. In mucosal disease, the presentation is nonspecific and is most related to location in the gastrointestinal tract. Most commonly, these patients’ manifestations include abdominal pain, nausea, vomiting, early satiety, and diarrhea. Malabsorption and failure to thrive are uncommon presentations that can occur in patients with extensive small-bowel disease. In patients with eosinophilic infiltration of the muscular layers (muscularis form), symptoms consistent with wall thickening and impaired motility predominate. These findings can be similar to symptoms associated with intestinal obstruction, including bilious vomiting and abdominal distention. Last, patients with involvement of the serosal layer can present with either isolated ascites or in combination with any of the symptoms noted previously herein in less infiltrative disease. (9) The ascites in such individuals typically contains a high eosinophil count (not present in this case), reflecting exudative cell loss via an inflamed

serosal surface (in contrast to the triglyceride chylous fluid found in this case). Of note, patients with serosal infiltration typically demonstrate a higher level of peripheral eosinophilia.

The differential diagnosis of EG includes intestinal parasites, malignancy, Crohn disease, hypereosinophilic syndrome, Langerhans cell histiocytosis, and other uncommon conditions that are usually distinguished from EG on the basis of clinical context and, when necessary, focused diagnostic tests.

The natural history of EG is highly variable and not well characterized. Some other allergic gastrointestinal disorders, such as infant dietary protein-induced enterocolitis and food protein-induced enterocolitis syndrome, typically resolve completely with age. However, based on small case series to date, EG is thought to generally follow a more chronic, persistent course, with periodic symptomatic flares in some affected individuals.

Chylous ascites occurs with the leakage of the milky-white, triglyceride-rich fluid into the peritoneal space. (10) Patients with CA present primarily with massive abdominal distention. In children, causes of CA include lymphatic anomalies, trauma, recent surgery, malignancy, and mycobacterial infection. The most common lymphatic anomaly that causes CA in children is intestinal lymphangiectasia, which is characterized by the dilation of subserosal enteric lymphatic. (11) This lymphatic obstruction can occur anywhere that lymph drainage takes place but favors the pulmonary and gastrointestinal systems. With obstruction of lymphatic vessels, lymph begins to flow into the pleural or peritoneal spaces. In the pleural space, this creates chylothorax, and in the peritoneal space, CA. (12) Lymphangiectasia can be a primary disorder or due to a secondary process that causes lymphatic obstruction. Secondary intestinal lymphangiectasia (SIL) is most commonly caused by congenital heart disease. (12) In our patient, SIL was likely due to gut inflammation obstructing the intestinal lymphatic drainage. Other causes include tuberculosis, Crohn disease, intestinal lymphoma, constrictive pericarditis, and more. (13) Also, SIL can be triggered by focal or diffuse bowel wall thickening, which may be caused by inflammatory processes, including gastroenteritis. (12)

DIAGNOSIS

Due to the nonspecific symptoms associated with EG, physicians must maintain a high index of suspicion in any patient with abdominal complaints and peripheral blood eosinophilia. (14) The latter is observed in more than two-thirds of patients with EG. Presently, there is no noninvasive way to definitively diagnose EG, and endoscopy with biopsy remains the gold standard for diagnosis. (15) Biopsy often

shows patchy eosinophilic infiltration of the gut wall and may reveal eosinophils in the crypts or villi. There are no established biopsy criteria for numbers of eosinophils necessary to make the diagnosis of EG, so the overall clinical context and subsequent course remain important contributors to the diagnosis. (16) Patients with ascites due to serosal involvement may undergo diagnostic paracentesis. (14) In patients whose food allergy is not known, skin prick tests and serum food-IgE levels can be used with varying success due to multiple immune responses involved in the disease process. (15)

Ascites must first be confirmed through imaging. (10) Ultrasonography seems to be the best imaging modality for the initial detection of ascites, especially in pediatric patients. Increasingly, ultrasonography may be performed by treating clinicians at the point of care, which may allow an earlier, more accurate diagnosis. (17)(18) Next, a sample of the fluid must be obtained. To diagnose CA, the fluid must have a triglyceride level greater than 200 mg/dL (>2.3 mmol/L) and a total protein level greater than 2.5 g/dL (25 g/L). (2) Elevated central venous pressure can cause lymphatic obstruction, which can trigger lymphangiectasia and CA. In infants this can develop from cardiac anomalies and must be ruled out by a transthoracic echocardiogram. (19) Patients suspected of having CA due to SIL can be diagnosed by imaging, pathology, or both. Abdominal computed tomography with contrast and noncontrast magnetic resonance lymphangiography have been used to make the diagnosis. On endoscopic biopsy, intestinal villi may appear cream-colored and edematous. Dilated lymphatic vessels may also be present. (12) Most often, SIL occurs in the jejunoleum, which can be out of reach of upper and lower endoscopy. As a result, endoscopy for SIL can often appear normal with no signs of dilated lymphatics. Capsule endoscopy has been suggested as the next diagnostic step for a negative endoscopic biopsy and clinical suspicion of SIL; however, it is currently not feasible in infants. (2)

MANAGEMENT

Although there is no standardized treatment for EG, a restricted and elemental diet has proved successful for many patients. Restriction requires that the patient eliminate the allergy-causing food from the diet, assuming the food allergen is known. Patients are then started on an elemental diet. For infants, this means starting an amino acid-based formula. With the implementation of a restricted and elemental diet, most patients see resolution of symptoms and serum eosinophilia within 3 to 6 weeks. (15) Corticosteroid therapy, which suppresses eosinophilic

inflammation, is used only in patients who are refractory to dietary changes (14) because corticosteroids must be given systemically to be effective and carry intrinsic adverse effects.

The first-line treatment for CA due to primary lymphangiectasia is a low-fat diet that is high in medium-chain triglycerides (MCTs). In contrast to long-chain triglycerides, MCTs do not need to be transported through the lymphatic system before reaching the circulation. Instead, MCTs are absorbed directly into the portal venous system. Octreotide is sometimes given as a long-acting somatostatin analog to reduce lymph flow in severe cases. (2) Treatment of SIL usually does not require an MCT diet as it often resolves with successful treatment of the underlying condition. (20) Operative treatment, including drainage and shunting, is attempted only if treatment of the underlying condition (SIL) or diet and medication (primary) fail to resolve the ascites. (10)

PATIENT COURSE

While admitted to the hospital, the infant passed regular stools and did not require further evaluation or treatment for constipation. She was discharged on a commercial elemental formula containing 100% amino acids and 33% of the fat blend as MCT oil. At her 2-month follow-up visit she was doing well, with complete resolution of the eosinophilia and ascites. Based on the prompt and sustained resolution of the CA and peripheral eosinophilia with elemental formula feeding, along with strongly supportive gut mucosal biopsy findings, her diagnosis is considered to be SIL due to inflammation from the EG. The subsequent clinical course of the patient has implied that the CA was not due to primary lymphangiectasia because the patient is now tolerating long-chain triglycerides without recurrence of symptoms.

Lessons for the Clinician

- In infants, a distended abdomen may reflect gaseous bowel loop distention, a mass lesion, or ascites, and imaging may be required to distinguish the cause.
- The nature of ascites, determined by paracentesis, may be critically important in leading to an appropriate diagnosis and management.
- Chylous ascites is an uncommon presentation of eosinophilic gastroenteritis. In patients with ascites and eosinophilia, a food allergy should be considered.
- Secondary intestinal lymphangiectasia is the dilation of lymphatic vessels due to another disease process. It usually resolves with treatment of the underlying problem.
- Ultrasonography is the best initial diagnostic tool to confirm ascites. Physicians trained in performing

ultrasonography at the bedside can help expedite patient care. (17)

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Case 6: Abdominal Distention and Constipation in a 70-day-old Female Infant

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Index of Suspicion

5

Abdominal Distention, Poor Growth, and Motor Delay in a 1-year-old Girl

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AUTHOR DISCLOSURE Dr McCarthy has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 1-year-old girl presents to the pediatrician's office with an enlarging abdomen since birth, poor weight gain since 6 months of age despite eating well, and developmental delay. She does not crawl or pull to stand and is unable to support herself on all fours for more than a few seconds. She was born at full term after an unremarkable pregnancy. She required a 3-day stay in the NICU for management of hypoglycemia, which resolved before discharge. She takes no medications and is up to date on immunizations.

At presentation she is afebrile and her heart rate is 122 beats/min, respiratory rate is 45 breaths/min, and oxygen saturation is 100% on room air. She is 26.2 in tall (66.5 cm, <1st percentile) and weighs 17.68 lb (8.02 kg, 17th percentile). She is tachypneic but appears comfortable, and lung sounds are clear. Her abdomen is protuberant and firm, and it is difficult to palpate the edge of the liver. Her legs are thin, with decreased strength and tone. She has normal verbal and fine motor skills for her age but has gross motor delays as described previously.

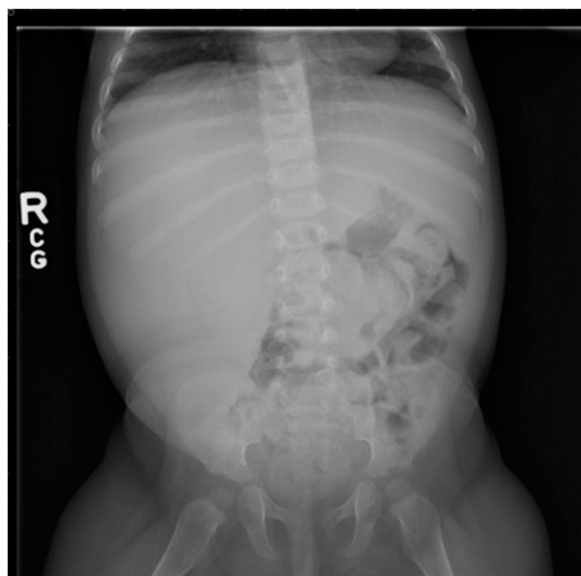


Figure. Abdominal plain radiograph showing hepatomegaly and centrally displaced loops of bowel.

Initial evaluation includes a chest radiograph, which is negative for any acute cardiopulmonary process but shows low lung volumes. Abdominal radiography reveals a markedly enlarged liver with the tip projecting over the right iliac crest (Fig).

Serum chemistry values are notable for sodium of 136 mEq/L (136 mmol/L), potassium of 4.1 mEq/L (4.1 mmol/L), chloride of 98 mEq/L (98 mmol/L), bicarbonate

of 11 mEq/L (11 mmol/L), glucose less than 20 mg/dL (<1.1 mmol/L), and lactic acid of 109 mg/dL (12.1 mmol/L). She is admitted to the hospital for management of severe hypoglycemia.

The Case Discussion and Suggested Readings appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/5/263>.

DISCUSSION

Based on the constellation of hepatomegaly, hypoglycemia, lactic acidosis, hypertriglyceridemia, hyperuricemia, and failure to thrive, a diagnosis of glycogen storage disease (GSD) is made on clinical grounds. Genetic testing confirms the diagnosis of GSD type Ib.

Condition

Glycogen storage disease type I is an autosomal recessive disorder with an estimated prevalence of 1 in 100,000. Deficiencies in glucose-6-phosphatase (type Ia) or glucose-6-phosphate translocase (type Ib) block both glycogenolysis and gluconeogenesis, leading to hypoglycemia and the accumulation of fat and glycogen in the liver and kidneys. Patients are at risk for sudden death due to hypoglycemia when fasting. The combination of hepatomegaly and hypoglycemia should lead the clinician to suspect GSD, particularly types 0, I, III, VI, and IX.

Patients with GSD I have a characteristic appearance with a doll-like face, plump cheeks, thin extremities, short stature, and a protuberant abdomen. Hepatomegaly and hypoglycemia typically develop at 3 to 6 months, although some newborns may have hypoglycemic episodes. After a meal, patients are often able to maintain their blood glucose levels for 2 to 4 hours, which can complicate the detection of hypoglycemia in infants who feed frequently.

Long-term complications of GSD I include short stature, osteoporosis, delayed puberty, chronic kidney disease, hypertriglyceridemia-induced pancreatitis, gout, and the development of hepatic adenomas that can undergo malignant transformation. Patients with GSD Ib have the additional risk of recurrent infections due to neutropenia and an increased incidence of inflammatory bowel disease and autoimmune hypothyroidism.

Diagnosis

The diagnosis of GSD I is confirmed either by detection of characteristic gene abnormalities or by liver biopsy with testing for glucose-6-phosphatase and glucose-6-phosphate translocase activity. After diagnosis, complete blood cell count, lipid profile, vitamin D level, platelet function assay, uric acid level, and liver and kidney imaging are all recommended to evaluate for associated complications and determine baseline levels. Siblings of the affected child should be evaluated as early as possible to avoid delays in treatment.

Treatment

Treatment of GSD I is primarily focused on dietary management to maintain adequate blood glucose, and a metabolic nutritionist should be consulted soon after the diagnosis. Frequent small meals that are high in complex carbohydrates and supplementation with uncooked cornstarch help provide a steady, slow-release source of glucose. Patients should also avoid fructose and sucrose and limit their intake of lactose and galactose. Appropriate nutrition mitigates many of the metabolic abnormalities and long-term sequelae of GSD I, although patients may still require treatment for gout, dyslipidemia, hypertension, and other complications. Liver transplant provides enzyme replacement and prevents lethal hypoglycemic episodes but does not address other affected organ systems. Patients must continue a modified diet, and many still go on to require renal transplant. Liver transplant is typically delayed as long as possible due to the potential for surgical complications.

Prognosis

With proper treatment, most affected individuals live to adulthood. Neurocognitive outcomes depend on the number of hypoglycemic episodes. Regular surveillance for osteoporosis, anemia, chronic kidney disease, dyslipidemia, and hepatic adenomas is recommended to ensure early recognition and intervention.

Lessons for the Clinician

- Glycogen storage disease (GSD) should be suspected in patients with hypoglycemia, hepatomegaly, and poor growth.
- Treatment of GSD I is focused on providing appropriate nutrition.
- Liver transplant prevents lethal hypoglycemia but has a high risk of complications.
- With proper treatment and surveillance, patients with GSD I have a good overall prognosis.

Suggested Readings

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Case 5: Abdominal Distention, Poor Growth, and Motor Delay in a 1-year-old Girl

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6 Abdominal Pain in a Recently Immigrated 10-year-old Girl

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AUTHOR DISCLOSURE Ms Hudson and Dr Blake have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 10-year-old previously healthy girl presents to the emergency department for evaluation of abdominal pain. Five days ago, she developed abdominal pain, which has been worsening. She has no history of fever, constipation, or diarrhea. She reports 4 episodes of nonbilious vomiting. There is no change in the color of her urine. She reports no other symptoms and denies any change in behavior. Her appetite and fluid intake are reported as increased, and she enjoys eating fast food every day. She has recently emigrated with her family from India to Canada. There is no significant family history of hemoglobinopathy or Wilson disease.

Physical examination reveals a weight of 118.4 lb (53.7 kg) (90th–97th percentile), height of 60.6 in (154 cm) (90th percentile), and BMI of 22.6 (90th–95th percentile). There is no evidence of hepatomegaly or jaundice. Abdominal examination reveals a soft abdomen with diffuse right upper quadrant tenderness and a negative Murphy sign.

Laboratory investigations reveal elevated aspartate aminotransferase (156 U/L [2.61 μ kat/L]) and alanine aminotransferase (81 U/L [1.35 μ kat/L]) enzyme levels, a normal amylase level (66 U/L [1.10 μ kat/L]), and an elevated urobilinogen level (19.4 mg/24 h [33 μ mol/d]). Her white blood cell count is elevated (17,100/ μ L [17.1 $\times 10^9$ /L]), with an increase in neutrophils (12,820/ μ L [12.82 $\times 10^9$ /L]). Her glucose level is within normal limits (109.9 mg/dL [6.1 mmol/L]), and she has a normal hemoglobin count (13.2 g/dL [132 g/L]). Hepatitis B surface antigen, heterophile antibody test, Epstein-Barr virus serology, and cytomegalovirus serology are negative.

Ultrasonography of the liver and gallbladder reveals a thin-walled gallbladder with multiple dependent, mobile, small gallstones. There are no findings suggesting perivesicular inflammation. The intrahepatic and extrahepatic bile ducts are not dilated or abnormal. There is no hepatic steatosis.

The Case Discussion and Suggested Readings appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/1/42>.

DISCUSSION

Gallbladder disease is uncommon in the pediatric population. The most common presentation of biliary colic in the pediatric population is biliary dyskinesia, which is a motility disorder affecting the gallbladder with no evidence of gallstones. However, the presentation of biliary colic due to gallstones has been increasing in the pediatric population, which was seen in the patient presented herein. Historically, evidence of gallstones in children and adolescents has been most often associated with hemolytic disorders. However, the frequency of gallstones in the absence of a hemolytic disorder has recently been on the rise in the pediatric population and has been associated with a high BMI. The development of gallstones due to a diet high in fat and obesity is multifactorial and is thought to include a high secretion of cholesterol and poor gallbladder motility.

The adoption of westernized diets on immigration to Canada, including an increased consumption of readily available fast foods, can have a negative effect on the health of immigrants. After moving to a foreign country, factors such as a higher level of stress, children's preferences, and a lack of traditional foods can result in a diet that is higher in fat and sugar, with larger portions and more consumption of convenience food. South Asian immigrants in Canada have reported an increase in the consumption of convenience foods, sugar-sweetened beverages, and red meat, as well as an increase in eating meals outside the home at convenient food establishments. These changes in dietary habits may result in an increase in BMI, which is known to be a risk factor for pediatric gallstone formation. Insulin resistance has also been described as a dietary risk factor for gallstone formation in children.

Cholesterol gallstones (70%–100% cholesterol) contain a higher amount of cholesterol than can be broken down by micelles in bile. They are most often the result of hypersecretion of cholesterol due to excess dietary intake and resulting increased hepatic uptake. Fat-rich food intake has also been identified as a risk factor for recurrence of gallstones.

Biliary colic is the most common symptom of gallstones, predominantly in the right upper quadrant of the abdomen. This biliary colic is often accompanied by nausea and vomiting. Nonspecific abdominal pain and irritability may be the only presenting symptoms, particularly in children younger than 5 years. Patients can present with cholangitis, choledocholithiasis, or pancreatitis, which is often accompanied by pain, fever, and jaundice. Gallstones may also be asymptomatic, in which case they are incidentally detected by ultrasonography.

Evaluation for suspected gallstone disease includes liver biochemistry as hepatic, alanine, and aspartate aminotransferase

levels, which are elevated early on in the obstruction. Serum bilirubin, alkaline phosphatase, and γ -glutamyl transferase levels elevate later in the course. A complete blood cell count often reveals a nonspecific elevated white blood cell count. Amylase levels are elevated when the patient has pancreatitis. Another important investigation in the diagnosis of gallstones is transabdominal ultrasonography, which can reveal gallstones, hepatobiliary duct dilatation, and pancreatitis. Suspicion of congenital ductal anomalies may be investigated best using magnetic or endoscopic retrograde cholangiopancreatography.

Management

Laparoscopic cholecystectomy is a safe and effective treatment option for biliary colic and gallbladder disease in the pediatric population. Furthermore, new evidence suggests that a same-day discharge after laparoscopic cholecystectomy is safe for pediatric patients, just as it is for adults. Cholecystectomy still remains an uncommon surgical procedure in the pediatric population; however, it is often performed in young female adolescents who are overweight or obese and have multiple gallstones. Resolution or improvement of preoperative symptoms after a laparoscopic cholecystectomy has been reported to be as high as 92.6% of patients undergoing the procedure. Complications of the procedure that were reported by a recent study include a prolonged ileus, wound infection, and the requirement for an incisional hernia repair. Comparison between same-day discharge and overnight hospital stay after the procedure found no differences in the complication rate, readmission, or follow-up before the scheduled appointment.

Patient Course

The patient is discharged from the emergency department on a 5-day course of a histamine-2 blocker (ranitidine), with outpatient follow-up arranged with a pediatric general surgeon. Repeated laboratory investigations 1 month later reveal that the previously elevated liver enzyme levels and white blood cell count have returned to normal. She is instructed to decrease the fat content of her diet, and an elective laparoscopic cholecystectomy is arranged.

Lessons for the Clinician

- Clinicians should be aware of the difficulty of dietary acculturation for newly immigrated patients.
- Preventive efforts should be made to provide education about healthy food choices and the danger of replacing fruits and vegetables with more convenient fast food.
- Newly immigrated children and adolescents may face negative health consequences that are not usually present in the pediatric population.

- Biliary colic and gallbladder disease should be considered with a presentation of right upper quadrant abdominal pain and raised liver enzyme levels.

Suggested Readings

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1 Abscess in a 9-year-old Boy

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EDITOR'S NOTE

We invite readers to contribute *Index of Suspicion* cases through the PIR manuscript submission system at: <https://mc.manuscriptcentral.com/pir>.

AUTHOR DISCLOSURE Drs Padem, Park, and Antoon have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 9-year-old Indian American boy presents to the clinic with buttock pain for 4 days. Associated symptoms include emesis and petechial rash for 2 days and intermittent confusion for 1 day. He has no history of surgical intervention, he is fully immunized, and his development is appropriate for his age. He was admitted to a PICU when he was 6 years old due to septic shock secondary to severe lymphadenitis. Family history is significant for asthma only. There is no family history of immunodeficiencies, severe infections, or early death. In a review of systems, the family report chronic dry cough for the previous few years.

In the clinic, the patient is found to be tachycardic, tachypneic, febrile, and mildly hypotensive. His oxygen saturation is normal on room air. Physical examination is significant for a buttock abscess and diffuse petechiae. Initial laboratory results demonstrate a normal complete blood cell count and basic metabolic profile and elevated levels of C-reactive protein, lactate, and coagulation factors (D-dimer and international normalized ratio). The patient is started on vancomycin and ceftriaxone. He is admitted to a PICU for further management.

On arrival at the PICU, he is noted to have hypotension. With a diagnosis of septic shock, he is started on epinephrine drip. Incision and drainage of a sacral abscess is performed, and wound cultures are positive for pan-susceptible *Staphylococcus aureus*. The patient improved and was discharged on oral antibiotics after a 6-day hospital stay. Concern for a second severe bacterial infection prompted an evaluation for possible immunodeficiency. Further laboratory testing reveals the diagnosis.

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/6/310>.

DISCUSSION

The Condition

Pertinent laboratory results during hospitalization include negative human immunodeficiency virus, negative QuantiFERON®-TB Gold (Quest Diagnostics, Secaucus, NJ), normal nicotinamide adenine dinucleotide phosphate oxidase activity by dihydrorhodamine assay, undetectable CH50, very low immunoglobulin (Ig) G, and undetectable IgA and IgM levels (Table 1). Given his capillary leak and active infection, several immunology laboratory tests were repeated a few days later, and values remained low. Despite the fact that he was up-to-date on his immunizations, testing for specific antibodies against vaccine-associated antigens, including tetanus and diphtheria toxoid, *Haemophilus influenzae* type b polysaccharide antigens, and *Streptococcus pneumoniae* polysaccharide antigens, were all negative (Table 1).

Lymphocyte marker analysis showed absent B cells. An in vitro lymphocyte mitogen stimulation study showed normal proliferative response. Genetic testing revealed W124R missense variant of the Bruton tyrosine kinase gene (*BTK*), confirming the diagnosis of X-linked agammaglobulinemia (XLA). The patient was started on intravenous immunoglobulin treatment every 4 weeks and remained free of infectious episodes 6 months after hospitalization.

X-linked agammaglobulinemia is a primary immunodeficiency characterized by abnormal B cell maturation and differentiation. It was first described by Bruton in 1952 and is the result of mutations involving the *BTK* gene. (1)(2)(3) Currently there are more than 300 mutations described, leading to highly variable presentations and disease courses. (4) X-linked agammaglobulinemia is a rare disease with an incidence of 1 in 379,000 live births in the United States. (5)

TABLE 1. Laboratory results at the time of diagnosis

| | RESULT | NORMAL | UNITS |
|---|--|----------|----------|
| IgG | 324 | 608–1572 | mg/dL |
| IgA | 3 | 34–274 | mg/dL |
| IgM | 11 | 38–251 | mg/dL |
| Specific antibodies to | | | |
| Tetanus toxoid, IgG | 0.0 | >0.1 | IU/mL |
| Diphtheria toxoid, IgG | 0.0 | >0.1 | IU/mL |
| <i>Haemophilus influenzae</i> B, IgG | 0.0 | >0.1 | IU/mL |
| Pneumococcal polysaccharide 23 serotypes, IgG | <0.3 | >1.3 | μg/mL |
| Isohemagglutinin titers | Absent anti-A (patient's blood group B+) | | |
| CH50 | | | |
| During sepsis | 0 | 60–144 | CAE |
| After resolution of sepsis | 103 | 60–144 | CAE |
| Lymphocyte subsets | | | |
| Absolute CD4 | 2349 | 430–1800 | cells/μL |
| Absolute CD3 | 6453 | 570–2400 | cells/μL |
| Absolute natural killer cells | 242 | 78–470 | cells/μL |
| Absolute CD19 | <1 | 91–610 | cells/μL |
| Neutrophil oxidative burst | Normal nicotinamide adenine dinucleotide phosphate oxidase activity by dihydrorhodamine assay | | |
| In vitro lymphocyte stimulation study | Normal lymphocyte responses to <i>Candida</i> , tetanus, phytohemagglutinin, con A, pokeweed mitogen | | |
| <i>BTK</i> gene mutation test | W124R missense variant in the <i>BTK</i> gene | | |

Ig=immunoglobulin.

Clinical Manifestations

The classic presentation of XLA consists of recurrent and/or severe infections after the loss of maternal immunoglobulins in blood at approximately 3 to 6 months of age. A report of data from 201 patients in the United States showed that the most common presentation or information that led to the initial diagnosis of XLA is increased susceptibility to infection (86%), followed by family history (41%). (5) The same study also showed that more than 50% of cases were symptomatic before age 1 year and 50% of cases were diagnosed as having hypogammaglobulinemia or agammaglobulinemia by 2 years of age. Patients with a family history of XLA were diagnosed earlier (mean, 2.59 years) compared with patients with no family history (mean, 5.37 years). Although the classical diagnosis age is in early childhood, there are case studies reporting presentation in adulthood. (6)

The most common infections associated with XLA are otitis media, pneumonia, sinusitis, diarrhea, conjunctivitis, sepsis, and cellulitis. One-third of XLA diagnoses are made after a severe infection, such as sepsis, meningitis, cellulitis, and empyema. (4)(5) Rarely, these patients may develop

vaccine-related paralytic poliomyelitis. (4)(7) Although immune modulation against viruses seems to be intact in XLA, echovirus infections are a well-known cause of encephalitis and meningitis in this population. (5)(6)(8)

Diagnosis

Diagnosis of XLA includes very low levels of all immunoglobulin isotypes, a very low number or absent B cells in peripheral blood, and molecular studies showing mutations in the *BTK* gene. Although lack of lymphoid tissue is a common feature of the disease, presence of lymphoid tissue does not rule out XLA diagnosis. (1)(11)(12)(13) The sentinel XLA case described by Bruton was a male child who underwent adenotonsillectomy and was found to have lymphoid and tonsillar tissue. Kornfeld et al (14) additionally reported a case with a history of adenotonsillectomy. Our patient was admitted to the hospital with severe lymphadenitis at 6 years of age and was noted to have lymphoid and tonsillar hypertrophy on physical examinations in his medical history, confirmed with CT scans and radiographic imaging at age 6 years (Figs 1 and 2).

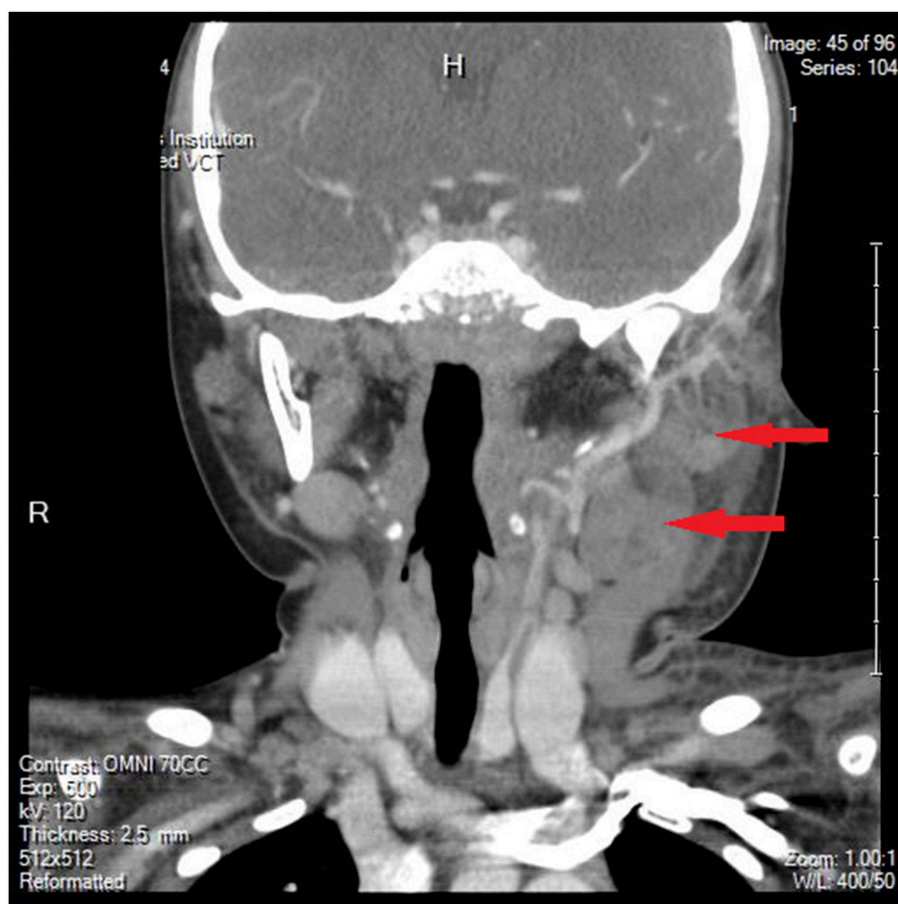


Figure 1. Lymphadenitis shown on a computed tomographic scan of the head and neck.



Figure 2. Lateral neck soft tissue radiograph with mildly prominent palatine tonsil and normal thickness of prevertebral soft tissue.

Delayed diagnosis of XLA can result in long-term chronic complications, such as bronchiectasis and other life-threatening infections. An immunologic evaluation was not performed for our patient when he was admitted to the hospital for sepsis secondary to lymphadenitis. The presented case highlights that the presence of lymphoid or tonsillar tissue and older age do not exclude XLA. This variation might be a result of multiple mutations of the *BTK* gene affecting disease process and presentation. Clinicians should have a high suspicion of XLA in male patients with severe or recurrent infections.

Management

A variety of malignancies are documented in patients with XLA, but a correlation between certain tumors and XLA has not been proved. (5)(9)(10) Treatment of XLA remains

immunoglobulin replacement with regular intravenous immunoglobulin or subcutaneous immunoglobulin infusions. Prophylactic treatment of infections with antibiotics remains controversial.

Lessons for the Clinician

- Patients with recurrent sinopulmonary infections, unexpectedly severe disease courses, or infections with uncommon pathogens at any age should be evaluated for primary immunodeficiency diseases, including X-linked agammaglobulinemia (XLA).
- Infections caused by live viral vaccines should also raise suspicion for immunodeficiency.
- Patients with XLA classically present with minimal lymph tissue and usually absent tonsillar tissue, but the presence

of lymphoid or tonsillar tissue should not exclude a diagnosis of XLA.

- Late diagnosis of XLA can result in early bronchiectasis, leading to worsening lung function, recurrent infections resulting in multiple hospital admissions, growth and development delay, missed school/work days, and eventually an increase in mortality.

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5 Acute Behavioral Changes in a 17-year-old Girl

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AUTHOR DISCLOSURE Drs Kader, Ngiam, and Kao have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 17-year-old girl is brought to the emergency department for unusual behaviors. On the day of presentation, her family members found her intermittently crying and talking to herself about angels, demons, redemption, and sins. She was speaking in a different voice and telling her family of "something evil within her." Her parents sought spiritual help from a priest, but this failed to improve her behavior. There were no recent changes in her mood, behavior, or academic performance.

The patient is overweight but otherwise well. For the past month she has taken slimming pills from an online store, but no other medications. She is a high-achieving student. She denies smoking, alcohol intake, or illicit drug use. There is no family history of psychiatric disorders.

On examination, she is clutching her crucifix, smiling, and laughing inappropriately. Her temperature is 98.6°F (37°C), heart rate is 101 beats/min, blood pressure is 120/61 mm Hg, respiratory rate is 18 breaths/min, and oxygen saturation is 99% on room air. Her weight is 167 lb (75.8 kg) (>97th percentile), height is 63.4 in (1.61 m) (75th-90th percentile), and BMI is 29.2. Her heart, lungs, and abdomen are normal. Findings from examination of the cranial nerves, tone, and reflexes are normal. She intermittently engages in conversation, describing multiple voices that interrupt her thoughts and tell her to hurt herself and her family.

She is admitted to the psychiatric ward. Laboratory test results, including a complete blood cell count; renal, liver, and thyroid function tests; complement 3 and 4 levels; ceruloplasmin levels; and urine drug screen, are normal. Further investigations reveal the diagnosis.

The Case Discussion and Suggested Readings appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/6/314>.

DISCUSSION

This girl has had an episode of acute psychosis, with auditory hallucinations, persecutory delusions, and thought interference.

The differential diagnosis of acute psychosis is broad. For such an acute onset, drug-induced hallucinosis must be considered. The initial urine analysis may be limited in the range of substances that can be tested for. Thus, any suspected substances that the patient is taking should be sent for further analysis.

Complex partial seizures may manifest as changes in behavior and affect and may be difficult to distinguish from primary psychiatric disorders. An electroencephalogram should be performed to determine whether episodes of unusual behavior correlate with seizure activity.

Although rarer and less likely, any cause of encephalopathy, including neurodegenerative disorders, space-occupying lesions (brain tumors, abscesses), demyelinating disorders (acute demyelinating encephalomyelitis, multiple sclerosis), and immune-mediated causes, such as anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis, may also be responsible for behavior changes and psychiatric symptoms.

Systemic medical conditions associated with neuropsychiatric manifestations include systemic lupus erythematosus; hyperthyroidism and hypothyroidism; metabolic disorders

such as Wilson disease and acute intermittent porphyria; infections such as human immunodeficiency virus and syphilis; and postinfectious syndromes. However, the clinical course is frequently of repeated episodes or progressive worsening. There are also often other physical signs or abnormal laboratory results to suggest the underlying etiology.

Finally, this may be the first presentation of a primary psychotic disorder such as schizophrenia, but this would be more likely to have a more chronic course. A brief psychotic episode—defined as a sudden onset of psychosis of less than 1 month and a full return to normal functioning thereafter—may be a possibility. The patient's cultural and religious background must also be considered when deciding whether a patient's beliefs are truly delusional.

A summary of these conditions and the relevant investigations are listed in the Table.

During her inpatient stay, the electroencephalogram showed a normal background and no epileptiform activity, even during her auditory hallucinations. She also underwent brain magnetic resonance imaging, with normal findings. Additional blood investigations for antistreptolysin O antibodies and anti-NMDA receptor antibodies were negative.

She is started on risperidone therapy but is discharged against medical advice 3 days later because her parents feel that the problem is spiritual rather than medical.

TABLE. Differential diagnoses for a first psychotic episode

| CONDITION | METHOD OF DIAGNOSIS |
|--|---|
| Neurologic | |
| Neurodegenerative disease | Brain magnetic resonance imaging |
| Space-occupying lesion (tumor, abscess) | Lumbar puncture (oligoclonal bands, <i>N</i> -methyl-D-aspartate receptor antibodies) |
| Demyelinating disease | |
| Immune-mediated encephalitis | |
| Systemic conditions with neuropsychiatric manifestations | |
| Systemic lupus erythematosus | Complements 3 and 4, anti-dsDNA |
| Hyperthyroidism/hypothyroidism | Thyroid function test |
| Wilson disease | Serum ceruloplasmin |
| Acute intermittent porphyria | Urine porphobilinogen |
| Infections (human immunodeficiency virus, syphilis) | Enzyme-linked immunosorbent assays for human immunodeficiency virus VDRL test for syphilis |
| Psychiatric | Psychiatric assessment |
| Schizophrenia | |
| Bipolar disorder | |
| Schizoaffective disorder | |
| Cultural | Explore patient's belief systems |

The slimming pills are sent to the Health Sciences Authority for further analysis. Although the pills were touted to contain only "all-natural ingredients," such as grapefruit and green tea, they are, in fact, found to contain undeclared amounts of sibutramine, a drug that has been banned in Singapore. A public health warning about the pills has been made in the local media.

The Condition

Many drugs are known to cause psychotic symptoms. The best known of these are alcohol and recreational drugs such as lysergic acid diethylamide (LSD), cocaine, cannabis, and amphetamines. However, other prescription drugs have been implicated as well, including opiates, selective serotonin reuptake inhibitors, barbiturates and benzodiazepines, clarithromycin, quinolone antibiotics, proton pump inhibitors, and sibutramine. Over-the-counter medications such as dextromethorphan and antihistamines at high doses have also been implicated in psychosis.

Sibutramine is a serotonin and norepinephrine reuptake inhibitor structurally related to the amphetamines. Its serotonergic action enhances satiety, and thus it had been marketed extensively as an anti-obesity agent. However, the Sibutramine Cardiovascular Outcomes (SCOUT) randomized controlled trial demonstrated increased risk of cardiovascular morbidity associated with sibutramine, confirming the concerns highlighted in previous case reports. Other common adverse effects of sibutramine include insomnia, dry mouth, constipation, nausea, and headache.

Sibutramine has since been withdrawn from the market in many countries around the world. Nevertheless, it is a common, undeclared ingredient in many weight-loss products that can be bought over the counter and from online stores. Examples of such products include "Slim Fit X," a product with a Food and Drug Administration (FDA) warning issued on July 27, 2016; "Zi Su Body Fat Health II," FDA warning issued on October 26, 2016; and "Nutri Drops Grapefruit Diet," warning issued in 2014. The dose of the drug in question should be checked if possible; there have been reports of illicit drugs in over-the-counter products being included in doses 3 or more times the recommended medical dose.

Sibutramine-associated psychosis has been well-documented in case reports and case series. The psychotic symptoms are attributed to increased dopamine levels due to reuptake inhibition, and the psychopathology includes manic episodes, delusional disorders, paranoid episodes, suicidal ideations, and catatonia. In a relatively large series from Hong Kong involving 16 patients, the most common psychiatric manifestations were auditory hallucinations, visual hallucinations, and persecutory ideations. These symptoms are self-remitting after stopping sibutramine use.

Management

A thorough evaluation for organic medical conditions associated with psychiatric manifestations should be performed. A comprehensive medication history inclusive of alternative, traditional, or over-the-counter substances and illicit drugs is of great importance. Such substances should be analyzed at a specialized laboratory to determine their constituents.

Treatment consists of immediate cessation of the offending agent(s). Antipsychotic agents may be used for a short period. Resolution within several days is expected, but patients should be followed up to ensure that psychotic symptoms do not recur.

To prevent further cases, the public must be educated about the risks of buying slimming products over the counter or from online sources and to be aware that such products often contain undeclared drugs that are hazardous to health.

On outpatient review 2 weeks after hospitalization, the patient's auditory hallucinations and delusions had resolved. She and her family have been informed about the contents of the slimming pills, and she has stopped taking these pills since her inpatient admission.

Lessons for the Clinician

- Drug-induced psychosis must be in the differential diagnosis for a patient presenting with acute psychosis.
- The differential diagnosis of psychotic symptoms is wide, and patients should be thoroughly evaluated for underlying medical causes before attributing the psychosis to a primary psychiatric disorder.
- The public must be made aware that substances banned by the health authorities may still be present in slimming products bought from online stores or over the counter.

Suggested Readings

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3 Acute Hypotonia, Hypothermia, and Altered Mental Status in a 10-month-old Girl

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AUTHOR DISCLOSURE Dr Beardmore has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. Dr Beardmore is now in private practice with SSM Health/Dean Pediatrics in Janesville, WI.

PRESENTATION

A 10-month-old previously healthy girl presents to the emergency department after being found unresponsive by her parents. The parents report she was a little fussy last night when they put her to bed, but it was not out of the ordinary. This morning she was found unresponsive to verbal or physical stimuli, completely limp, and blankly staring, and they immediately rushed her to the hospital. She has no medical problems, takes no medication, has had regular follow-up with her pediatrician, and all her shots are up to date. She has been hospitalized only once previously, a less than 3-day stay before turning 1 month old, for a fever and to rule out sepsis. She was then discharged with normal laboratory values and only 2 days of antibiotic drug therapy for a presumed viral illness.

On arrival at the emergency department her immediate general assessment shows her eyes open and blankly staring, with complete loss of tone. Her vital signs include rectal temperature of 95.3°F (35.2°C), heart rate of 100 beats/min, respiratory rate of 30 breaths/min, pulse oximetry of 100% on room air, and blood pressure of 123/77 mm Hg. Her heart examination findings are normal, and her capillary refill is not prolonged. She has normal nonlabored respirations with clear breath sounds, and her abdomen is soft without organomegaly or masses palpated. Her conjunctivae are without pallor, and her mucous membranes are moist. Her anterior fontanelle is open and flat, not bulging or sunken, and she has no neck stiffness. Her pupils are mid-sized and do not respond to light. She has a blink reflex to light but not to visual threat. She has only minimal whimper to sternal rub. All 4 extremities are floppy, with 0/5 strength, and she has complete head lag when her torso is lifted. Her deep tendon reflexes are normal. Her secondary survey shows no bony or joint deformities, swellings, or other abnormalities; her skin examination findings are normal, without lesions, ecchymosis, or areas of erythema; her genitourinary examination findings are also normal. Initial laboratory investigations and follow-up history reveal the diagnosis.

The Case Discussion and Reference appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/6/312>.

DISCUSSION

The first laboratory test performed on this hypothermic child with altered mental status was a finger-prick glucose test (to which she did not react or withdraw), and the value was 18 mg/dL (1 mmol/L). A peripheral intravenous line was placed, and during the administration of 50 mL (5 mL/kg) of dextrose 10% in water (D10W) she began to first blink, then voluntarily move extremities, then cry, and by the end of the infusion, in a matter of only a few minutes, she was looking and reaching for her parents. Further questioning elicited that the paternal grandmother lives in the home and has type 2 diabetes, and the father states that he found spilled tablets on the floor in the home 2 days ago. When the child was stable, the father was able to go home and procure the medicine he had cleaned up. The bottle label showed that it was 10-mg glipizide. It was, therefore, assumed that the father must have missed 1 or more of the spilled tablets when cleaning up and the child was able to find and ingest 1. This hypothesis was strengthened when the follow-up glucose values improved and then dropped again, improving to 201 mg/dL (11.2 mmol/L) after the first D10W bolus and dropping again to 41 mg/dL (2.3 mmol/L), although she stayed asymptomatic at this value.

The Condition

Hypoglycemia caused by ingestion of a sulfonylurea is due to endogenous insulin release. Sulfonylureas inhibit potassium channels of pancreatic β cells, leading to intracellular potassium increase, depolarization of the cell, calcium influx, and, finally, insulin release from the pancreas. The time to peak onset, the half-life, and the duration of action of sulfonylureas are specific to each drug, and for glipizide they are approximately 1 to 3 hours, 2 to 5 hours, and 16 to 24 hours, respectively. (1) Octreotide is the antidote to this because it works as a semisynthetic somatostatin analog that inhibits pancreatic insulin release. The appropriate dose in children is 1.0 to 1.5 μ g/kg per dose given intramuscularly, subcutaneously, or by intravenous bolus, repeated every 6 hours for the expected duration of action of the ingested drug. (1)

When correcting hypoglycemia with an intravenous bolus, whatever the cause, a good rule to remember is the rule of 50s. That is, in a formula multiplying dextrose percentage by volume in milliliters per kilogram, the value

should always equal 50: $D \ a \% \times b \text{ mL/kg} = 50$, choosing a percentage a and solving for b . In our case, choosing D10W resulted in a need for 5 mL/kg, so for a 10-kg child, the bolus is 50 mL. If D5W were chosen, a volume of 10 mL/kg would equal the rule number of 50, and thus for a 10-kg child, the bolus would need to be 100 mL, which may be preferred if increasing intravascular volume would also be helpful.

Management and Patient Course

In consult with the toxicologist before the grandmother's medication could even be determined, the child's case presentation was suspicious for ingestion of a sulfonylurea. After rebound hypoglycemia to a glucose level of 41 mg/dL (2.3 mmol/L), which required a second D10W bolus in addition to continuous dextrose infusion, and confirmation of the spilled glipizide in the home, the toxicologist recommended octreotide subcutaneous injection, a total of 5 μ g/kg divided into 4 injections, spaced every 6 hours, to cover the expected maximum of 24 hours of duration of action. The child received her first injection in the emergency department and was admitted to the ICU for mental status and glucose level monitoring. Owing to her hypothermia on arrival, which improved along with the immediate correction of her hypoglycemia, laboratory testing was conducted to rule out serious bacterial infection at the time of the initial presentation, and all the results were normal, including a negative blood culture. The child was discharged after 24 hours, after the last octreotide injection, without a further episode of hypoglycemia and without a return of altered mental status.

Lessons for the Clinician

- Blood glucose is often a valuable initial test when evaluating a child with altered mental status.
- Altered mental status from hypoglycemia can be accompanied by significant neurologic findings and hypothermia.
- Uncovering the cause of the hypoglycemia is of utmost importance for treatment purposes and should, thus, include a detailed and thorough history.

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Case 3: Acute Hypotonia, Hypothermia, and Altered Mental Status in a 10-month-old Girl

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6 An Infant Presenting with Hematuria and Pallor

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AUTHOR DISCLOSURE Drs Riney, Treasure, Varnell, and Depinet have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 5-month-old healthy boy presents to our pediatric emergency department with parental concerns of blood in the urine and yellow appearance of the skin. His medical history and birth history are normal. The patient has had nonbloody diarrhea for the past 2 weeks that resolved 2 days ago. He has had 1 episode of nonbilious nonbloody emesis the previous day. In addition, he has had decreased oral intake and increased fussiness for the previous 2 days. His mother noticed a red-brown discoloration in the front of the diaper yesterday and yellow discoloration of the skin, prompting her to present to the pediatric emergency department.

Vital signs at presentation are heart rate, 157 beats/min; respiratory rate, 42 breaths/min; blood pressure, 127/70 mm Hg; and rectal temperature, 97.9°F (36.6°C). On initial examination in the emergency department, the patient is pale but alert, active, in no apparent distress, and playful. His mucous membranes are moist, and his oropharynx is normal, without lesions. The cardiovascular examination reveals a regular rate and rhythm, without murmurs, rubs, or gallops. He has strong peripheral pulses and good distal perfusion. His pulmonary examination findings are normal. His abdomen is soft, nondistended, and nontender, with normal bowel sounds. Neurologic examination shows symmetric normal strength and tone with grossly intact cranial nerves and no deficits. Skin examination shows generalized pallor but no rash or petechiae. Both feet seem to be mildly edematous.

Pertinent laboratory studies in the emergency department show a white blood cell count of $27,200/\mu\text{L}$ ($27.2 \times 10^9/\text{L}$) (reference range, 6,000–17,500/ μL [6.0–17.5 $\times 10^9/\text{L}$]), with 38% segmented neutrophils and 2% bands; a hemoglobin level of 3.7 g/dL (37 g/L) (reference range, 10.5–13.5 g/dL [105–135 g/L]); a hematocrit level of 10% (reference range, 33%–39%); and a platelet count of $38 \times 10^3/\mu\text{L}$ ($\times 10^9/\text{L}$) (reference range, $13.5 \times 10^3/\mu\text{L}$ – $46 \times 10^3/\mu\text{L}$ [$\times 10^9/\text{L}$]). In addition, the blood smear shows 2+ schistocytes, 1+ ovalocytes, and 1+ teardrops. The renal panel is significant for a potassium level of 6.9 mEq/L (6.9 mmol/L) (reference range, 3.2–6.3 mEq/L [3.2–6.3 mmol/L]), a blood urea nitrogen level of 59 mg/dL (21.1 mmol/L) (reference range, 6–17 mg/dL [2.1–6.1 mmol/L]), and a creatinine level of 0.95 mg/dL (72.44 $\mu\text{mol/L}$) (reference range, 0.16–0.39 mg/dL [12.20–29.74 $\mu\text{mol/L}$]).

The hepatic profile is normal. The urinalysis was significant for large blood and large protein with 10 to 14 white blood cells and greater than 50 red blood cells per high-power field and 2+ bacteria.

Because of severe anemia, thrombocytopenia, hyperkalemia, and acute kidney injury, the patient is admitted to

the PICU and the nephrology team is consulted. Additional studies lead to the diagnosis.

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/2/98>.

DISCUSSION

While in the PICU, further laboratory studies showed a lactate dehydrogenase level of 1,704 U/L (28.5 μ kat/L) (reference range, 155–450 U/L [2.6–7.5 μ kat/L]), a haptoglobin level less than 7 mg/dL (<70 mg/L) (reference range, 16–200 mg/dL [160–2,000 mg/L]), a reticulocyte count of 5.3% (reference range, 0.5%–1.5%), a C3 complement level of 1.24 g/L (reference range 0.624 g/L–1.84 g/L), and ADAMTS13 activity of 92% (reference range, >67%). The stool culture grew *Escherichia coli* O157:nonH7 and Shiga toxin 2 three days later. The urine culture showed no growth after 5 days. A diagnosis of hemolytic uremic syndrome (HUS) was made.

The Condition

Hemolytic uremic syndrome is a type of thrombotic microangiopathy, a heterogeneous group of diseases that have common clinical manifestations, including microangiopathic hemolytic anemia, thrombocytopenia, and organ injury. (1)(2) Classically, HUS presents as severe abdominal pain and diarrhea, often bloody, that begins several days after consumption of food contaminated with Shiga toxin–producing *E coli* (STEC). (3) Hemolytic uremic syndrome should be suspected in any pediatric patient with recent abdominal pain and diarrhea followed by thrombocytopenia and anemia 5 to 7 days later. (1) Other clinical signs during this period may include hypertension, oliguria, central nervous system manifestations, altered mental status, and possibly more severe gastrointestinal manifestations (ischemic bowel or intussusception). (4) After a few more days, anuria may develop, and the clinical picture can change to include coma, cerebral infarcts, cranial nerve dysfunction, seizures, and even death. (2)(4) Laboratory studies that should be performed on presentation are as follows: a complete blood cell count, a peripheral blood smear, renal function studies, and urinalysis. (5) Other initial testing includes coagulation studies (to differentiate from disseminated intravascular coagulation) and stool studies for Shiga toxin and cultures. (5) Shiga toxin–producing *E coli* accounts for almost 90% of all cases of HUS, with occurrence usually younger than 5 years, most being older than 6 months. (2)(3)

History has shown that young children and elderly people can have substantial impairment from infection with STEC. (6) Approximately 5% to 10% of people with STEC infection will go on to develop HUS, and 50% of those will have some degree of renal impairment after disease. (2)(6) The severity of the acute illness and the need for initial dialysis are strongly linked to a poor long-term prognosis. (7) Hemolytic uremic syndrome should be considered for any child with a history of resolving diarrhea now with concern for kidney injury given that it is a common cause of acute renal failure worldwide. (8)

Diagnosis

The diagnosis of HUS is based on laboratory findings, although it does require a certain level of clinical suspicion, particularly given a well-appearing child with only a history of previous diarrheal illness. The most common laboratory findings are hemolytic anemia, thrombocytopenia, and renal dysfunction. (9) More specifically, the anemia found in HUS is a normochromic-normocytic anemia, with an average hemoglobin level of 8 g/dL (80 g/L). (4) Additional laboratory findings that are often seen include azotemia, a decreased haptoglobin level, an elevated C-reactive protein level, hematuria and/or proteinuria on urinalysis, an increased lactate dehydrogenase level, leukocytosis, an elevated reticulocyte count, and a negative Coombs test result. (9) The first signs of renal involvement are typically hypertension, (seen in nearly 50% of patients with HUS), hematuria, and proteinuria. (4) Severe renal disease is characterized by anuria and renal failure. (4) More commonly, however, patients experience a brief period of oliguria (median of 7 days) with associated electrolyte abnormalities, including hyponatremia, hyperkalemia, metabolic acidosis, hyperphosphatemia, and hypocalcemia. (4) A stool culture should be obtained in any patient suspected of having HUS to evaluate for the presence of STEC, which is a reportable illness and has implications for morbidity and mortality. (9)

Stool cultures were sent as well as enzyme immunoassay for Shiga toxin 1 and Shiga toxin 2 to assess for STEC-HUS. ADAMTS13 activity was sent to assess for thrombotic thrombocytopenic purpura (TTP) and in our patient was normal. The other major consideration in this patient was atypical HUS (aHUS). Given that the patient's disease was relatively mild on hospital admission, with a stable elevated creatinine level and good urine output, aHUS genetic testing was deferred unless the testing for Shiga toxin came back negative. Current diagnostic criteria for aHUS are a serum creatinine level at or above the upper limit of normal, microangiopathic hemolytic anemia, thrombocytopenia, ADAMTS13 activity of 5% or more, and negative stool tests for Shiga toxin–producing infection. Our patient's stool culture was positive for *E coli* O157:nonH7 and Shiga toxin 2, thus, further treatment was supportive in nature.

Differential Diagnosis

In a pediatric patient presenting with a recent diarrheal illness, the differential diagnosis is broad and includes viral or bacterial gastroenteritis, colitis, inflammatory bowel disease, or intussusception. (9) In a pediatric patient presenting with laboratory findings of severe anemia, thrombocytopenia, and concern for acute kidney injury, the differential diagnosis is relatively narrow. Three diseases that were initially considered that could describe the patient's presenting symptoms include HUS, aHUS, and TTP.

By definition, aHUS is not preceded by the characteristic bloody diarrhea of STEC infection, but because most cases of aHUS involve dysregulation of the complement system it is frequently triggered by an infectious event, including gastroenteritis with diarrhea. (10) Commonly, TTP, which is rare in children, is caused by congenital mutation in the *ADAMTS13* gene, a plasma metalloprotease that cleaves von Willebrand factor. (1)

Management

There are no known cures for HUS, and management is primarily supportive. Given the wide range of illness severity, it is important that patients diagnosed as having HUS are closely monitored for anemia, electrolyte disturbances, and acute renal failure. Fluid balance before and after the development of HUS has been shown to be important in limiting the severity of renal failure and the need for dialysis. (9) The decision to start dialysis is based on the ability to correct renal failure and electrolyte abnormalities with fluid replacement alone. (4) Approximately 50% of patients will require dialysis at some point during the illness, with approximately 7.6% going on to require dialysis long-term. (8) In addition, studies have shown that more than 90% of patients diagnosed as having HUS will require a blood transfusion during the course of the illness. (8) Regarding the finding of thrombocytopenia in HUS, platelet transfusions are not routinely given due to the worsening of the thrombotic cascade, and platelet function typically normalizes after several weeks. (4) Interestingly, the use of antibiotics has been studied in patients diagnosed as having HUS and in some studies has been shown to actually increase the incidence and complications of HUS when given during the diarrheal stage of the illness. (2)(3) The worsening of disease is believed to be secondary to the release of large amounts of bacterial toxins with the use of antibiotics. (2)(3)

Patient Course

During his PICU admission, the patient remained hemodynamically stable. He was given calcium chloride 10 mg/kg intravenously for cardiac membrane stabilization. He was kept nothing per os and started on 10% dextrose 1/2 normal saline for insensible losses at 10 mL/kg as well as replacement fluids for urine output every 6 hours. Furosemide 2 mg/kg was given intravenously due to hyperkalemia and concern for blood transfusion exacerbating his hyperkalemia. Slow correction of anemia was performed to prevent massive hemolysis. He was given 2 intravenous transfusions of packed red blood cells 5 mL/kg each. No antibiotics were given. No antihypertensives were needed because the systolic blood pressure remained less than 130 mm Hg and trended down during the

admission, although still elevated for his age. Daily weights were obtained, strict intake and output were recorded, and nephrotoxins were avoided. He had good urine output during his admission. He was transferred from the PICU after 2 days to the nephrology service and was discharged after 5 days.

The patient had return of normal renal function at his nephrology outpatient visit 48 days after his initial diagnosis of Shiga toxin–positive HUS. Blood pressure was 82/50 mm Hg, which was 37 percentile systolic for age and 88 percentile diastolic for age, based on the 2000 National Health and Nutrition Examination Survey data. Laboratory studies showed normalization of his electrolytes, blood urea nitrogen, creatinine, hemoglobin, and platelets. Urinalysis was negative for proteinuria and hematuria. He had no evidence of chronic kidney disease at further follow-up visits with the nephrology service.

Lessons for the Clinician

- Hemolytic uremic syndrome is one of the most common causes of acute renal failure in the pediatric population worldwide, and its rising incidence makes it an important diagnosis to consider. (11)
- Although hemolytic uremic syndrome is a disease with specific laboratory criteria, the wide variance of clinical presentations and multiple etiologies of the illness can make it difficult to diagnose.

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Case 6: An Infant Presenting with Hematuria and Pallor
Lauren C. Riney, Jennifer D. Treasure, Charles D. Varnell Jr and Holly Depinet
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4 Atypical Cause of Cyanosis While Bathing in an 18-month-old Boy

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AUTHOR DISCLOSURE Drs Maurice and Ellsworth have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An 18-month-old boy with a medical history of cyanotic episodes presents with possible seizure activity at child care. When he was 10 months old, 8 months before presentation, he began having periods when he would become limp and cyanotic for a minute. The episodes would occur when bathing. There was no eye deviation noted, or shaking of extremities. Initially the episodes occurred once per month but have become more frequent, now with each occurrence of bathing. He has presented to an outside hospital, and was evaluated with brain magnetic resonance imaging and electroencephalography (EEG), which, per report, were reassuring, and he was discharged with no medications to follow up with a pediatrician. On the day of admission he had an episode of seizurelike activity, described as tonic-clonic activity of his upper and lower extremities, followed by a period of being nonresponsive and foaming at the mouth. This occurred after washing his hands at child care.

In the emergency department he is well appearing with normal vital signs. Evaluation includes a normal complete metabolic panel (including electrolyte levels and renal and liver function) with negative urine drug screen and head computed tomographic scan results. An inpatient test reveals the diagnosis.

DISCUSSION

While an inpatient, the patient undergoes video EEG with the addition of water exposure. During video EEG, the patient is given a sponge bath with his feet in water. The EEG recordings show intermittent theta frequency slowing, most prominently over the left centrottemporal region. When the mother places the patient's feet in water and begins to bathe him with a wet towel, the EEG shows simultaneous changes described as higher-amplitude delta frequency slowing over the left temporal region. This activity then spreads to involve the left frontocentral and temporal regions, followed by evolution with higher-amplitude and faster-frequency sharp waves or spike/wave activity, most prominent over the left frontotemporal region, consistent with epileptic activity. Clinically he initially has decreased responsiveness followed by decreased tone.

The Condition

This case highlights an uncommon cause known as reflex epilepsy triggered by the stimulus of hot water, or bathwater. Reflex seizures are seizures that are

triggered by internal or external stimuli. This type of seizure composes 4% to 7% of those with epilepsy. (1) The trigger for reflex seizures can include visual (such as the flashing lights from video games), auditory, proprioceptive, and somatosensory stimuli, or even hot water. In general, the simple triggers, such as flashing lights, will trigger a seizure within seconds, whereas the more complex cognitive tasks, such as reading, will take minutes to trigger a seizure. (2) Bathing epilepsy is a rare type of reflex epilepsy in which the seizures are provoked from both tactile and heat stimuli. (3) It was first described in 1945, and since that time case series of patients have been reported around the world, with large numbers of patients from southern India, Japan, and Turkey. (4) Males are more commonly affected (2.6–3:1), and the range of age at onset is from 7 months to 13 years. (5) In a collection of 18 cases, the onset of seizure activity ranged from the time the patient touched the water to 60 seconds after initiation of bathing. (6)

Diagnosis

The diagnosis of bathing epilepsy first requires a history that would direct toward the diagnosis. Many patients have pallor, cyanosis, and hypotonia near the onset of bathing. To

definitively diagnose this reflex epilepsy over other bath-induced paroxysmal disorders would require a video EEG during a bath.

Management

The first line of management is to decrease the temperature of the water, as that alone can resolve the seizures for some. For those who do not respond to lower-temperature water or changing the method of bathing, antiepileptic medications (frequently carbamazepine) can be initiated. (7)

Lessons for the Clinician

- Bathwater epilepsy can be a source of bathing-induced hypotonia and cyanosis.
- The diagnosis is confirmed using video electroencephalography while triggering a seizure.
- The first line of treatment is to decrease the temperature of the water; the second line is to administer antiepileptic medications.

References for this article are at <http://pedsinreview.aappublications.org/content/39/11/568>.

Case 4: Atypical Cause of Cyanosis While Bathing in an 18-month-old Boy

Rachel Maurice and Misty Ellsworth

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Case 4: Atypical Cause of Cyanosis While Bathing in an 18-month-old Boy

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1 Breast Development in a 2-year-old Girl

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EDITOR'S NOTE

We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: <https://mc.manuscriptcentral.com/pir>.

AUTHOR DISCLOSURE Ms Logan and Dr Kingery have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 2-year 10-month-old girl presents with precocious puberty. Her parents recently noticed breast development and vaginal discharge described as “lotion” in her underwear. They deny any exposure to exogenous sources of estrogen. She does not take any medications or have any significant medical history.

Anthropometrics are notable for height of 37.6 in (95.6 cm) (74th percentile), weight of 31.5 lb (14.3 kg) (65th percentile), blood pressure of 82/51 mm Hg, and heart rate of 95 beats/min. Physical examination findings are remarkable for bilateral breast buds consistent with Tanner stage 2, with Tanner stage 1 pubic and axillary hair, and pink vaginal mucosa consistent with estrogenization. Skin examination is significant for the absence of café-au-lait spots.

Laboratory values obtained at presentation reveal normal thyroid function. Luteinizing hormone and follicle-stimulating hormone levels are prepubertal at 0.1 mIU/mL (0.1 IU/L) and less than 0.2 mIU/mL (<0.2 IU/L), respectively. Estradiol level is elevated at 108.6 pg/mL (398.7 pmol/L). On transabdominal pelvic ultrasonography she has a postpubertal uterine size and shape but normal ovarian volumes for age without evidence of a tumor. Her bone age is advanced at 3 years 10 months. Tumor markers are negative. No lesions consistent with fibrous dysplasia are seen on skeletal survey. Findings from brain magnetic resonance imaging and computed tomography of the abdomen and pelvis are normal. A gonadotropin-releasing hormone (GnRH) stimulation test indicates a prepubertal response.

Repeated laboratory studies performed 5 days after initial presentation reveal that her estradiol level decreased to 35.4 pg/mL (130.0 pmol/L). Further history reveals the diagnosis.

DISCUSSION

Four months after her initial presentation, the patient's estradiol level has decreased further to 8.8 pg/mL (32.3 pmol/L). On physical examination, breast buds have decreased in size, with minimal glandular tissue, and her vaginal mucosa has a red, beefy appearance. Her parents share that the girl's grandmother uses vaginal estrogen cream. The girl had been residing at her grandmother's house while her parents were away to adopt her younger brother. Since she lost access to the cream after her parents' return home, her symptoms have virtually resolved.

Exogenous Estrogen Exposure

Exogenous sources of estrogen are suggested by the history, laboratory values, imaging findings, and near-complete resolution of symptoms. Decreasing estradiol levels support this diagnosis; other pathologies, such as tumors and gonadotropin-dependent precocious puberty (GDPP), or central puberty, typically intensify over time.

Children are particularly sensitive to even small variations in levels of sex steroids. (1) Breast tissue size correlates with circulating levels of estradiol, especially early in life—this sensitivity is present in both girls and boys. (1) Similarly, estradiol has a biphasic effect on bone growth. (1) At low levels, estradiol stimulates linear growth via epiphyseal growth; at high levels, it causes cessation of linear growth via epiphyseal plate closure. (1) It is suggested that estradiol is the primary hormone driving pubertal growth in both girls and boys. (1) Thus, estrogen promotes both increased linear growth velocity and advancement of bone age in children.

Diagnostic Procedures

The keys to diagnosis in this case are a good history and the diminishing estradiol levels. Decreasing estradiol levels in association with gradual resolution of symptoms fostered the likelihood of previous exposure to exogenous estrogen that had subsequently been removed from her environment.

In addition to low gonadotropin levels, the patient's negative response to GnRH stimulation testing makes GDPP unlikely. Measurable or stimulated gonadotropin levels with GnRH stimulation in a child are consistent with GDPP. Pelvic ultrasonography can be helpful to evaluate for increasing ovarian volumes consistent with central stimulation, as well as to rule out ovarian pathologies for precocious puberty such as tumors. Pelvic ultrasonography also allows for evaluation of uterine and endometrium volume, which increases with estrogen exposure. A brain magnetic resonance image to assess for pathology, such as tumors or pituitary abnormalities, is indicated with biochemical evidence of GDPP. However, most GDPP in girls is idiopathic.

An elevated estradiol level in the presence of low gonadotropin levels is suspicious for either peripheral or exogenous estrogen exposure. Tumor markers, pelvic ultrasonography, and computed tomography of the abdomen and pelvis are each useful in detecting an estrogen-producing mass, which can cause estrogenization in the absence of measurable gonadotropin levels. Although primary hypothyroidism with high circulating levels of thyrotropin is a cause of precocious breast development, the patient had normal thyroid function laboratory values.

Differential Diagnosis

In girls with peripheral or gonadotropin-independent precocious puberty (GIPP), an ovarian mass is only one of many differential diagnoses. Long-standing primary hypothyroidism associated with vaginal bleeding and breast development is termed *Van Wyk-Grumbach syndrome*. (2) Girls with primary hypothyroidism may also present with galactorrhea and short stature with primary hypothyroidism. (3) Although a functional ovarian cyst is the most common cause of GIPP, recurrent episodes of breast development and vaginal bleeding would raise the suspicion of McCune-Albright syndrome, which is associated with the classic triad of multiple café-au-lait spots, fibrous dysplasia, and GIPP. (4) If the patient's vaginal discharge had a foul odor, a foreign body should be suspected, although these patients typically do not have breast development or elevated estradiol levels. (5) Last, concern for sexual abuse may be raised in any child with genital complaints, especially vaginal bleeding in the absence of breast development. (6)

Treatment

In most cases of exogenous hormone exposure, removal of the causative agent from the environment allows for regression of induced hormonal effects, as observed in our patient. However, it does not negate the potential long-term complications resulting from exogenous sex steroid exposure early in life; these may include compromised adult height, psychosocial trauma, or increased risk of certain cancers in adulthood. (1)

Lessons for the Clinician

- Although gonadotropin-independent precocious puberty (GIPP) is an uncommon cause of precocious puberty in girls, it is important to recognize because management and expected clinical course vary significantly based on etiology.
- GIPP resulting in examination findings consistent with estrogenization include benign and malignant gonadal tumors, McCune-Albright syndrome, primary hypothyroidism, and exogenous sex steroid exposure.
- Exogenous sex steroid exposure should be considered in any child presenting with gonadotropin-independent precocious puberty.
- Even if parents deny the possibility of exogenous sex hormone exposure, it should remain on the differential diagnosis until definitely excluded. Although sensitive and potentially uncomfortable, it is important to encourage the parents to query each caretaker about potential personal use of exogenous steroids.

References for this article are at <http://pedsinreview.aappublications.org/content/39/12/612>.

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Case 1: Breast Development in a 2-year-old Girl

Lauren Logan and Suzanne E. Kingery

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1 Concurrent Upper Respiratory Tract Infection and Vulvar Ulcers in a Teenage Girl

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EDITOR'S NOTE

We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: <https://mc.manuscriptcentral.com/pir>.

AUTHOR DISCLOSURE Drs Chu, Genisca, and Kaziny have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 13-year-old previously healthy white girl presents to the emergency department (ED) with 6 days of worsening cough and sore throat, 5 days of fever (highest temperature 102.5°F [39.2°C]), and painful red papules that have progressed to deep ulcers on her labia minora (Fig 1). The sores are painful to the touch, with worse pain during urination. The patient denies sexual activity, urinary frequency or urgency, pruritus, or hematuria. The last time she shaved her genital region was several months earlier. At symptom onset, she had several episodes of dizziness, with standing as well as nonbilious, nonbloody emesis, which have now resolved. Acetaminophen and ibuprofen have been given for fever. Miconazole and zinc oxide creams were used for the vulvar symptoms and did not help. She saw her primary pediatrician 2 days ago and a laboratory evaluation was performed, but the parents do not know the results.

On arrival at the ED the patient's temperature is 98.4°F (36.9°C), blood pressure is 106/65 mm Hg, heart rate is 111 beats/min, and respiratory rate is 16 breaths/min. Her genitourinary examination reveals 3 deep ulcers with ragged edges and clean bases just lateral to the right labia near the introitus that are painful to the touch. No erythema or inflammation of the labia or surrounding region is noted. The remainder of her physical examination findings are normal.

Review of the electronic medical record showed that the patient's pediatrician had tested her via the rapid influenza diagnostic test, rapid strep test, and spot test for infectious mononucleosis, all of which had negative results. The pediatrician also tested for *Candida*, *Trichomonas*, and bacterial vaginosis via a genital swab; these were negative as well.



Figure 1. Photographs of the patient's initial genitourinary examination. Red arrows indicate the ulcerative lesions.

In the ED the patient tested negative for gonorrhea and chlamydia by urine polymerase chain reaction (PCR), herpes simplex virus (HSV) by serum PCR and by genital swab quantitative PCR, and syphilis by treponemal antibody. A wound culture taken from the base of 1 of the ulcers grew abundant mixed urogenital flora. A fungus culture from the vaginal discharge was negative. Of note, the patient's Epstein-Barr virus (EBV) antibody panel results were as follows: immunoglobulin (Ig) M, less than 10 U/mL; IgG, 483 U/mL (<18

U/mL negative); and EBV nuclear antigen, 134 U/mL (<18 U/mL negative), indicating that the patient had been infected with EBV in the past but did not have an active infection at this time. The characteristics of the ulcers combined with the negative laboratory results confirmed the diagnosis.

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/5/258>.

DISCUSSION

The Condition

Lipschütz ulcers are also referred to as acute genital ulcers, acute vulvar ulcers, primary aphthous ulcers, and *ulcus vulvae acutum*. They were first described in a case series by Benjamin Lipschütz, a dermatologist and microbiologist, in 1913. (1) To this day they remain a relatively rare and unknown condition, and few cases are published in the pediatric literature. These ulcers present as exquisitely painful, well-defined lesions with a necrotic base on the labia majora, labia minora, perineum, or lower vagina or at the introitus. Ulcers can be single or multiple. Dysuria is usually present, although other symptoms of a urinary tract infection are absent. The typical patient is a prepubertal or pubertal teenage girl, often without any sexual history, who also presents with symptoms of an upper respiratory tract infection (fever, malaise, pharyngitis, tonsillitis, lymphadenopathy, myalgias, headache, cough, congestion). (2)(3)(4)(5) The youngest patient reported in the literature was 17 months old at the time of diagnosis; (6) multiple case reports detail this diagnosis in adult women as well. (2) The condition is most commonly associated with EBV, although case reports have also implicated cytomegalovirus, *Mycoplasma*, *Parvovirus*, *Salmonella typhi*, and mumps. (2)(7) Often, no infectious etiology is identified.

The pathophysiology of Lipschütz ulcer is unknown. One possibility is that EBV infects the B lymphocytes, which then circulate throughout the body, causing a direct cytotoxic effect in the epithelial cells of the genital tract. (3)(4) Alternatively, the condition may be due to immune complex formation secondary to a hypersensitivity reaction to a viral or bacterial infection, with deposition of immune complexes leading to microthrombosis and necrosis at sites distant from the original infection. (2)

Diagnosis

The differential diagnosis of a prepubertal or pubertal teenage girl presenting with vulvar ulcers includes sexually transmitted diseases (STDs), specifically HSV. A detailed sexual history is warranted, as well as STD testing, to rule out any treatable causes. At minimum, testing for HSV is indicated, and testing for other STDs may be performed based on history and physical examination findings. Furthermore, a careful history and thorough examination evaluating for autoimmune causes of genital ulcers, including Behçet disease, Crohn disease, and pyoderma gangrenosum, must be performed. In the setting of negative STD test results, low suspicion for autoimmune disease, and concurrent symptoms of upper respiratory tract infection, a

diagnosis of Lipschütz ulcers can be made. Biopsy of the ulcer is not recommended if clinical suspicion for Lipschütz is high because pathology findings are nonspecific and the procedure, thus, inflicts pain to the patient with no evident benefit.

Management and Patient Outcome

The patient was discharged from the ED with lidocaine jelly for symptomatic relief. A phone call was made to the patient's home 1 month after her ED visit. The patient's outcome was discussed with her father, who stated that the lidocaine jelly provided relief for the ulcer pain. The ulcers slowly shrank in size and then eventually resolved over the 2 to 3 weeks after her ED visit. Her cough persisted for 3 to 4 weeks and was symptomatically relieved with an over-the-counter cough syrup. The patient is now well and back to her baseline.

Lessons for the Clinician

- Lipschütz ulcer should be on the differential diagnosis of a teenage girl who presents with vulvar ulcers, especially in the presence of a concurrent upper respiratory tract infection.
- A thorough history and physical examination should be performed to evaluate for sexually transmitted and autoimmune diseases. Laboratory evaluation is left to clinical suspicion, but herpes simplex virus testing is recommended. A biopsy is not necessary.
- Ulcers resolve spontaneously within 2 to 3 weeks, and only supportive therapies are needed.

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4 Diffuse Rash in a 2-month-old Girl

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AUTHOR DISCLOSURE Drs Dean, Geraghty, and Real have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A former 32-week-gestation, now 8-week-old girl presents to her primary care clinic with a diffuse rash. The rash started at 4 weeks of age as a single lesion on her right thigh. The rash subsequently spread throughout her lower extremities. The mother brought the patient to the clinic at 6 weeks of age for the rash, which had crusted over. The patient was diagnosed as having bullous impetigo and was prescribed oral cephalexin and topical mupirocin. A wound culture from that visit grew normal skin flora. Her rash continued to worsen. The patient presents today for her 2-month well-child check with persistent rash.

On physical examination, the patient's vital signs are within normal limits. Her rash is most prominent on the trunk and lower extremities. The rash appears as scattered, well-defined erythematous papules and pustules with overlying scale and several erythematous nodules. It involves the palms and soles and spares the diaper region (Fig 1). Other than the rash, she is doing well, with no fevers, fussiness, lethargy, or abnormal movements. She is growing appropriately and meeting her developmental milestones. Her mother denies anyone else at home with a rash. Of note, her mother's prenatal infectious laboratory test results were negative, including syphilis.

Preliminary laboratory evaluation reveals a negative treponemal immunoglobulin G/M, a negative human immunodeficiency virus antigen/antibody

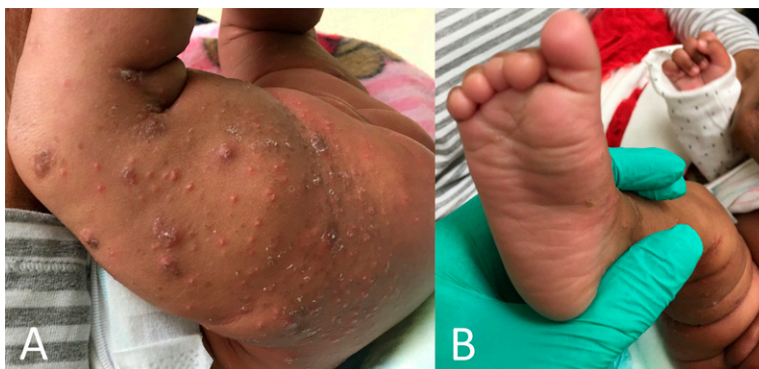


Figure 1. A. Erythematous papules, pustules, and nodules with overlying scale. Rash is most prominent on the lower extremities, with the diaper region spared. B. Crusted lesion on the plantar surface of the right foot.

screen, and a normal complete blood cell count. A telephone call with her mother the following day helps make the diagnosis.

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/4/214>.

DISCUSSION

While discussing the reassuring laboratory results, the patient's mother disclosed that although no one else at home currently had a rash, the family had an outbreak of scabies 3 months earlier for which the patient's 6 siblings and parents were all appropriately treated. Our patient was prescribed permethrin 5%. At a follow-up examination 1 week later, her rash was dramatically improved (Fig 2).

The Condition

Scabies is a parasitic skin infection caused by the *Sarcoptes scabiei* mite, common in overcrowded living situations. Mites can live both on and off the human host, including in clothing, bedding, furniture, and carpeting. It classically presents with a pruritic, papular rash involving interdigital webs on the hands, the flexor surface of the wrists, the extensor surface of the elbows, the abdomen, the axilla, and the genitalia. The rash is secondary to inflammatory and hypersensitivity reactions to the mite. The presence of burrows, serpiginous lines that are formed from the breakdown of mite digestive products, can be pathognomonic for this diagnosis. (1)

Neonatal scabies often has a markedly different presentation than scabies in older children or adults. It typically presents with diffuse vesicles, papules, and pustules; lacks burrows; and does not involve the interdigital web spaces. In addition, scabies in neonates rarely presents with obvious

pruritus due to the patient's age. It has a similar presentation to other disease processes, which can lead to a delay in diagnosis or misdiagnosis altogether. (2) The differential diagnosis includes impetigo, folliculitis, congenital infections including syphilis and herpes simplex virus, papular urticaria, infantile acropustulosis, eczema, and Langerhans cell histiocytosis. (1)(2)(3)(4)

Congenital syphilis was a concern in this case owing to the location and appearance of the rash. Newborns with congenital syphilis are usually asymptomatic at birth and begin showing signs by 5 weeks of age. The first sign is typically rhinitis ("snuffles"), followed by a diffuse, desquamating maculopapular rash involving the palms and soles. Syphilitic pemphigus is a common finding that is manifested by a vesiculobullous rash that crusts over after 1 to 3 weeks and can mimic neonatal scabies. (5)(6)(7) A key differentiating factor is rash distribution, with congenital syphilis often including the diaper region and neonatal scabies often sparing it.

Diagnosis

Neonatal scabies can be diagnosed using a variety of methods. Most commonly, it is a clinical diagnosis that requires a high index of suspicion. Close contacts diagnosed as having scabies or with severe pruritus often aid in making the diagnosis. The gold standard for diagnosis is direct visualization of the scabies mite or eggs, which can be done via potassium hydroxide scraping of a burrow (if present) or skin biopsy. (1)(8)



Figure 2. Appearance of the rash at follow-up 1 week after treatment with permethrin 5%.

Complications

A diagnosis of scabies can cause significant psychological and emotional distress for families, which should be addressed by providers. (1) The most common serious complication from scabies is a secondary bacterial infection, often caused by group A *Streptococcus* (GAS) or *Staphylococcus aureus*. Secondary infections caused by GAS have led to outbreaks of glomerulonephritis and rheumatic heart disease. (1)(4)(8) Postscabies pruritus, which can last for weeks to months, is another common complication. It is the result of a hypersensitivity reaction that can lead to excoriations causing dyspigmentation. Postscabies nodules are similarly caused by a hypersensitivity reaction and can persist for weeks. Families should be counseled and reassured about these common complications because they are often misinterpreted as reinfestation. (1)(2)(8)

Management

The standard treatment for scabies in adults and children aged 2 months and older is permethrin 5% cream applied once at bedtime for 8 hours, with an additional application as needed 1 week later. (1)(2)(8) A recent Cochrane review confirmed permethrin 5% as the most effective topical treatment for scabies. (8) Serious adverse effects to permethrin 5% are extremely rare. (1)

For children younger than 2 months, the recommended treatment is 10% topical sulfur in petroleum. (2)(4) However, this product must be compounded and can be difficult for some families to access. Due to the minimal risks associated with its use, some providers choose to use permethrin 5% in children younger than 2 months. (2) There are additional topical and oral treatment options for scabies that are generally less preferred due to inferior efficacy and significantly worse adverse effect profiles compared with permethrin 5%. (8) To prevent recurrence, all family members should be treated with at least 1 application

of permethrin 5%. In addition, all bedding, clothing, and towels should be washed in hot water, and furniture and carpeting should be vacuumed. (1)(2)(8)

Lessons for the Clinician

- Neonatal scabies is characterized by diffuse vesicles, papules, and pustules and, unlike scabies in older children and adults, often lacks burrows or involvement of the interdigital web spaces.
- Neonatal scabies often spares the diaper region, which can differentiate it from the rash associated with congenital syphilis.
- Mites can live both on and off the human host, including in clothing, bedding, furniture, and carpeting, necessitating inquiry about remote infestations when scabies is on the differential diagnosis.
- In children aged 2 months and older, permethrin 5% is the most effective topical treatment for scabies.

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Case 4: Diffuse Rash in a 2-month-old Girl
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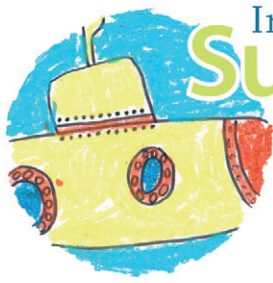
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Index of Suspicion

3

Emesis and Oral Hyperpigmentation in a 17-year-old Girl

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AUTHOR DISCLOSURE Drs Fredette and Topor have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 17-year-old girl presents for evaluation of persistent emesis and an unintentional 13.2-lb (6-kg) weight loss during the past 3 months. Emesis occurs daily in the mornings and is nonbloody and nonbilious. Nausea improves throughout the day and with hot showers. She denies diarrhea. When eating, she prefers salty foods such as pickles. She reports daily marijuana use. She feels that marijuana has stained her lips and tongue, as they appear darker to her. She notes fatigue, epigastric pain, weakness, and dizziness. She denies fevers, dysuria, or headaches.

On physical examination she is afebrile, with a heart rate of 140 beats/min, respiratory rate of 18 breaths/min, blood pressure of 86/52 mm Hg, and oxygen saturation of 98%. Her weight is 91 lb (41.3 kg) (<1st percentile), height is 59 in (150 cm) (2nd percentile), and body mass index is 18.3 (14th percentile). Patchy hyperpigmentation is noted on the lips, buccal mucosa, and palate. Bowel sounds are hyperactive, and abdominal examination is without tenderness, rebound, or guarding. There are no masses or hepatosplenomegaly.

Laboratory evaluation reveals a low serum sodium level of 130 mEq/L (130 mmol/L), with a normal potassium level of 3.8 mEq/L (3.8 mmol/L). Urine pregnancy test result is negative. The results of thyroid function testing, liver enzymes, lipase, complete blood cell count, and inflammatory markers are within normal limits. Abdominal radiograph is normal. Additional laboratory testing reveals the diagnosis.

DISCUSSION

Random serum cortisol and corticotropin samples were sent in the setting of hypotension and tachycardia, and a stress dose of hydrocortisone (90 mg/m² per day) was administered given concern for primary adrenal insufficiency (PAI). She received normal saline intravenous fluids for volume resuscitation. Her serum cortisol level was low at 1.3 µg/dL (35.9 nmol/L) (normal range, 5.5–20 µg/dL [151.7–551.8 nmol/L]), and her corticotropin level was elevated at 3,156 pg/mL (694 pmol/L) (normal range, 9–57 pg/mL [2–13 pmol/L]), diagnostic of PAI.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for recurrent emesis, abdominal pain, and weight loss with associated symptoms of fatigue and weakness is vast and includes conditions such as pregnancy, eating disorders, acute infections or inflammatory disorders, gastrointestinal obstruction or gastroparesis, cyclic vomiting syndrome, cannabinoid hyperemesis syndrome, increased intracranial pressure, and adrenal insufficiency. Our patient had a history of frequent marijuana use and improvement in nausea with hot showers, which supports a diagnosis of cannabinoid hyperemesis syndrome. However, her findings of oral hyperpigmentation, salt craving, and electrolyte abnormalities were worrisome for an alternative diagnosis of PAI. Cannabinoid hyperemesis is a syndrome of severe cyclic vomiting accompanied by abdominal pain in individuals who use marijuana frequently. Symptoms are temporarily alleviated by hot showers and baths, and patients may report compulsive bathing for symptom relief. The pathophysiology is unclear, but proposed mechanisms include dysregulation in endogenous cannabinoid receptors in the brain and gastrointestinal tract. Definitive treatment is abstinence from cannabis use. (1)

Hyperpigmentation of the oral cavity is classically seen in PAI, but it can also be physiologic. (2) Physiologic oral hyperpigmentation occurs in dark-skinned individuals and darkens with age and with smoke exposure. Tobacco smoke exposure itself can cause hyperpigmentation, typically seen in the gingiva. Oral hyperpigmentation can also be seen as a postinflammatory reaction to oral infections or trauma or after foreign body exposure to lead or amalgam. (3) Peutz-Jeghers syndrome is associated with mucocutaneous hyperpigmentation but is accompanied by intestinal polyposis and increased cancer risk. Most individuals with this autosomal dominant clinical syndrome have mutations found in the tumor suppressor gene *STK11* and have a higher risk of intrainestinal and extraintestinal malignancies, including gastrointestinal, breast, ovarian, pancreatic, cervical, testicular, and lung cancers, among others. These individuals are also at risk for severe bleeding, obstruction, and intestinal infarction due to large numbers of hamartomatous polyps in the gastrointestinal tract, most commonly in the small intestine. In this condition, blue to black macules are characteristically seen on the vermilion border of the lower lip but are also found intraorally and periorally on the hands and feet, as well as surrounding the eyes, nose, and perianal region. Macules are not present at birth, typically appear in infancy, and often fade during puberty. Intraoral macules often persist into adulthood. (4)

THE CONDITION

Primary adrenal insufficiency, commonly referred to as Addison disease, results from the failure of the adrenal cortex to produce adequate cortisol and aldosterone. The signs and symptoms can be nonspecific, with insidious onset including fatigue, weight loss, mood changes, abdominal pain, nausea, vomiting, and weakness. Salt craving, as well as electrolyte abnormalities, including hyponatremia, hyperkalemia, hypercalcemia, and hypoglycemia, can be present. In women, axillary and pubic hair may be sparse due to low adrenal androgen production.

Low cortisol levels in PAI stimulate production of corticotropin and other pro-opiomelanocortin cleavage products, such as melanocyte-stimulating hormone. An elevated melanocyte-stimulating hormone level triggers melanin production, resulting in the classic hyperpigmentation of the skin and mucous membranes found in PAI. Hyperpigmentation is typically generalized but is most easily identified in mucous membranes, skin creases, and scars. With treatment, the corticotropin levels decline, and the diffuse hyperpigmentation typically improves. (5)

In contrast, secondary adrenal insufficiency is due to insufficient corticotropin production, which leads to cortisol deficiency without hyperpigmentation. Salt craving and hyperkalemia are also absent in secondary adrenal insufficiency, as aldosterone production is intact.

Up to 90% of adult patients in developed countries with PAI have autoimmune adrenalitis, diagnosed with autoantibodies to adrenal enzymes such as 21-hydroxylase. In pediatrics, genetic forms constitute most cases, the most common being congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Alternate etiologies of PAI include adrenal hypoplasia, X-linked adrenoleukodystrophy, metabolic disorders, infections, infiltrative disorders, neoplasms, and hemorrhage. (6)

The diagnosis of PAI is suggested by a serum morning cortisol level less than 5 $\mu\text{g/dL}$ (<140 nmol/L) in combination with a corticotropin level greater than 2-fold the upper limit of the reference range. If clinical circumstances allow, confirmatory testing with a corticotropin (synthetic corticotropin) stimulation test is used. In the stimulation test, 250 μg of intravenous corticotropin is administered to individuals 2 years or older, 125 μg to individuals younger than 2 years, and 15 $\mu\text{g/kg}$ to infants. (7) Cortisol levels are measured 30 and/or 60 minutes after infusion. Diagnosis of adrenal insufficiency is confirmed if the peak cortisol level is less than 18 $\mu\text{g/dL}$ (<500 nmol/L) 30 or 60 minutes after injection. (7)

Undiagnosed PAI can present acutely in adrenal crisis when a patient is subjected to severe stress, major illness, trauma, or surgery. Adrenal crisis is a life-threatening state with signs including abdominal pain, vomiting, hypotension, severe electrolyte abnormalities, shock, and even death. Treatment of adrenal crisis should not be delayed while awaiting confirmatory results.

MANAGEMENT

Maintenance treatment of PAI requires both glucocorticoid and mineralocorticoid replacement therapy, as well as stress dosing of corticosteroids with acute illness, trauma, or surgery. The typical dose of maintenance glucocorticoid replacement is hydrocortisone 8 to 10 mg/m² per day divided 3 times daily. Typical stress dosing is hydrocortisone 50 to 100 mg/m² per day divided 4 times daily and administered every 6 hours. During stress dosing, maintenance glucocorticoid and mineralocorticoid replacement is held. Typical mineralocorticoid dosing in the pediatric population is 0.1 to 0.2 mg of fludrocortisone daily. Salt should not be restricted, and in infants, salt supplementation may be required.

PATIENT COURSE

Tachycardia, hypotension, electrolyte abnormalities, and emesis improved within 24 hours of treatment, and she

transitioned to maintenance hydrocortisone and fludrocortisone at discharge. She and her family received education about her diagnosis and the indications for stress dosing of corticosteroids.

Lessons for the Clinician

- Oral and skin hyperpigmentation, a specific sign of Addison disease, is a clue to the diagnosis of primary adrenal insufficiency (PAI) in an individual with otherwise vague symptoms, including gastrointestinal complaints, weakness, dehydration, and fatigue.
- Diagnosis of PAI is suggested by a serum morning cortisol level less than 5 µg/dL (<140 nmol/L) combined with a serum corticotropin level greater than 2-fold the upper limit of the reference range. Confirmatory testing is with corticotropin stimulation testing, with peak cortisol levels less than 18 µg/dL (<500 nmol/L) at 30 or 60 minutes.
- Given the life-threatening nature of adrenal crisis, if you are considering adrenal insufficiency with acute adrenal crisis as a top diagnosis on your differential diagnosis list, start treatment with a stress dose of corticosteroids while awaiting diagnostic studies to return, ideally serum cortisol and corticotropin levels.

References for this article are at <http://pedsinreview.aappublications.org/content/39/8/421>.

Case 3: Emesis and Oral Hyperpigmentation in a 17-year-old Girl

Meghan E. Fredette and Lisa Swartz Topor

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2 Epigastric Pain in a 14-year-old Boy

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AUTHOR DISCLOSURE Drs Berlin, Weisgerber, and Loonto have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 14-year-old boy with a medical history significant for mild intermittent asthma presents to the emergency department with 5 days of epigastric pain, chest pain, poor oral intake, and subjective fevers. On initial presentation he is diagnosed as having viral gastritis and is sent home from the emergency department with an antiemetic drug and instructions for supportive care. However, his symptoms worsen and he is referred back to the emergency department by his primary care physician, ultimately resulting in his admission. The patient is afebrile on presentation, with age-appropriate vital signs. Physical examination findings are normal except for discomfort with deep palpation of his epigastric region. Results of initial evaluation (including abdominal radiography, blood cell count, electrolyte levels, liver function testing, lipase levels, and urinalysis) are within normal limits. Therefore, the initial concern is for a combination of gastritis and constipation: he is treated symptomatically without improvement.

As symptoms persist, he is unable to tolerate any oral intake due to pain and eventually requires placement of a nasogastric tube to maintain proper nutrition. He notes that his most prominent pain localizes to the substernal region. In addition, he begins complaining of odynophagia. A thorough review of the patient's history reveals an isolated episode of food impaction approximately 1 year earlier and a father with significant gastroesophageal reflux disease complicated by an esophageal stricture at age 20 years. The patient remains afebrile, with repeated laboratory work and imaging findings within normal limits.

Given odynophagia and substernal chest pain, the differential diagnosis shifts toward an esophageal pathology, although the differential diagnosis for his suspected esophagitis remains large. A family history of esophagitis and a personal history of food impaction are commonly reported with eosinophilic esophagitis (EoE). However, the acute onset of his condition with reported fever suggests possible infectious etiologies, such as *Candida albicans* and herpes simplex virus (HSV). Finally, significant gastroesophageal reflux disease (GERD) resulting in erosive esophagitis is considered. Pill esophagitis and other etiologies of corrosive esophagitis are also considered, but the patient denies any such ingestion.

Direct visualization with biopsy is required. Gastroenterology is consulted, and the boy undergoes endoscopy, which reveals significant ulceration of the lower esophagus. At this point, concern for EoE is so significant that he is given

intra-procedural intravenous methylprednisolone and is immediately started on daily oral fluticasone as presumptive treatment for EoE. Additional testing reveals the true diagnosis.

DISCUSSION

The biopsies taken during endoscopy show substantial neutrophilic inflammation, with only 0 to 2 eosinophils noted per field, effectively ruling out EoE. Corticosteroids are immediately stopped, and the dose of his proton pump inhibitor is increased, as GERD becomes the most likely diagnosis. After 2 days, testing and culture for HSV returns positive, confirming the diagnosis of HSV esophagitis.

Clinical Course and Management

The patient is started on acyclovir therapy (800 mg 3 times daily) and has improvement in symptoms. He is discharged from the hospital with 10 days of acyclovir and a nasogastric tube in place to facilitate feeding. He improves substantially on this regimen, and tube feedings are quickly discontinued as his odynophagia resolves. He follows up with gastroenterology 4 weeks after discharge; at this time he denies any odynophagia or chest pain, and his weight loss has resolved.

The Condition

Herpes simplex virus esophagitis is increasingly becoming recognized as an etiology of infectious esophagitis in both immunocompetent and immunosuppressed individuals. Most commonly, this disease process occurs with the primary infection of HSV in a host. Generally, there is local spread of HSV from an orolabial or pharyngeal source directly to the esophagus. This was likely the case in the present patient, as he had been sharing drinks with his mother—who had an open cold sore—about a week before his admission.

Herpes simplex virus type 1 is the most common cause, although HSV2 has been implicated. Previous research has suggested that the disease process is more likely to occur in the presence of esophageal pathology (such as severe GERD or biopsy sites) as the virus is more likely to infect traumatized tissue, although there are many cases—including our patient—where there is no identified damage to the mucosal integrity.

Typically, HSV esophagitis presents with acute odynophagia and retrosternal chest pain, as in this patient. The classic patient is an otherwise healthy male younger than 40 years. Oropharyngeal or genital ulcers are generally absent (reported to be present in less than one-quarter of cases).

Many patients report a similar prodrome of fever and malaise but can also report respiratory symptoms or sore throat.

Endoscopy is required for diagnosis and should reveal ulcerated lesions in the distal one-third of the esophagus. Biopsy should be performed, preferably at the ulcer edge. Pathologic examination can show a neutrophilic inflammation, eosinophilic intranuclear inclusions, or multinucleated giant cells. Polymerase chain reaction and culture should confirm the diagnosis of HSV esophagitis.

Differential Diagnosis

The differential diagnosis for esophagitis can be separated into 3 broad categories: infectious, eosinophilic, and erosive. Erosive esophagitis includes pill esophagitis and erosive esophagitis secondary to GERD. There is a multitude of medications associated with pill esophagitis, including medications that change the tone of the lower esophageal sphincter (such as opioids or anesthetics) or pills that cause direct mucosal injury, such as nonsteroidal anti-inflammatory agents, potassium chloride, or ferrous sulfate. Eosinophilic esophagitis is characterized by mucosal inflammation secondary to eosinophilic infiltration of esophageal squamous mucosa. The classic patient presenting with EoE is one with a history of atopy (including asthma, such as in our patient) and a history of food impaction. Typically, patients will also have a family history of either EoE or significant GERD. Given the patient's presentation, EoE was very high on our differential diagnosis list. However, biopsy would show many eosinophils per high-power field in the case of EoE.

Infectious esophagitis can be secondary to fungal pathogens (most commonly *Candida*), viruses, or bacteria. The most common infectious etiologies are *C. albicans*, HSV, and cytomegalovirus. *Candida* esophagitis can be seen in either immunocompetent or immunocompromised hosts and presents with multiple white plaques in the esophagus. Cytomegalovirus esophagitis is seen almost entirely in immunocompromised patients. Finally, HSV esophagitis can be seen in either immunocompromised or immunocompetent patients but is much more likely in the immunocompromised patient.

Treatment and Prognosis

In immunocompetent patients, HSV esophagitis is typically a self-limited disease. Acyclovir should be offered to all patients because it may speed recovery, although the true benefit of antiviral therapy is unknown at this time. Supportive care, including good nutrition, is important. Finally, all patients should have underlying immune conditions

(specifically human immunodeficiency virus) ruled out because this condition is still much more common in those with immunodeficiency.

Lessons for the Clinician

- Consider esophageal pathology early in a patient presenting with odynophagia and chest pain.

- Herpes simplex virus esophagitis can occur in immunocompetent hosts and should be considered in the differential diagnosis of esophagitis.

Suggested Readings for this article are at <http://pedsinreview.aappublications.org/content/39/11/562>.

Case 2: Epigastric Pain in a 14-year-old Boy
Kathryn Elizabeth Kaye Berlin, Michael Weisgerber and Elizabeth Loconto
Pediatrics in Review 2018;39;562
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Case 2: Epigastric Pain in a 14-year-old Boy

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1 Eye Discharge in a 10-day-old Neonate Born by Cesarean Delivery

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EDITOR'S NOTE

We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: <https://mc.manuscriptcentral.com/pir>.

AUTHOR DISCLOSURE Drs Singh, Galvis, and Das have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 10-day-old boy presents with discharge from the left eye. It started at 3 days of age as a continuous, clear discharge and became copious and mucopurulent at 7 days of age. The mother reports swelling over the left eye, which started 2 days ago, and it worsened gradually so that he is not able to open his left eye today. The mother denies fever, trauma, sick contacts, recent travel, or rash. The patient was born at term via cesarean delivery. Maternal history is significant for a *Trichomonas vaginalis* infection during the second trimester, which was adequately treated. All other prenatal test results were negative. Review of the nursery records revealed that the patient received erythromycin prophylaxis for conjunctivitis.

On admission, he is afebrile and his vitals are stable. Physical examination shows a fussy neonate with eyelid swelling and erythematous conjunctiva with mucopurulent discharge from the left eye. The remaining physical examination findings are normal.

Initial laboratory evaluation shows a normal complete blood cell count and serum electrolyte levels. His human immunodeficiency virus (HIV) antibody test as well as rapid plasma reagin test results are negative. The cerebrospinal fluid (CSF) analysis results are normal. Additional evaluation leads to the diagnosis.

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/4/210>.

DISCUSSION

The differential diagnosis of injected conjunctiva with eye discharge (conjunctivitis) in the neonatal period includes chemical conjunctivitis, chlamydia conjunctivitis, gonococcal conjunctivitis, and trauma. Gram-stain of the discharge from the left eye of our patient showed gram-negative diplococci, which were confirmed to be *Neisseria gonorrhoeae* on culture. Chlamydia polymerase chain reaction was negative. Blood, urine, and CSF cultures were sterile.

The patient was initially started on intravenous ampicillin and cefotaxime pending culture results. The antibiotics were discontinued after 48 hours when the blood, urine, and CSF cultures were reported to be negative. However, after the culture result from the left eye was confirmed to be *N gonorrhoeae*, the patient was treated with a single dose of ceftriaxone and underwent scheduled irrigation of both eyes. The patient was evaluated by a pediatric ophthalmologist to ensure that he has not developed the complications of gonococcal conjunctivitis, and none were identified. The patient responded well, with complete resolution of the swelling and mucopurulent discharge. The mother and her partner were requested to get evaluated and treated for sexually transmitted infections (STIs).

The Condition

Ophthalmia neonatorum (ON), also called neonatal conjunctivitis, is a broad term and includes all forms of acute, mucopurulent infection of the eyes in the first 4 weeks of life. Up to 12% of newborns are affected by ON. In the past (before the 1880s), the term ON was used only for cases of

conjunctivitis caused by infection with *N gonorrhoeae* and was the primary cause of neonatal blindness. (Table)(1)

Epidemiology

Chlamydial infections are the most common bacterial cause of conjunctivitis in neonates, accounting for up to 40% of cases of neonatal conjunctivitis. *Streptococcus pneumoniae* and nontypeable *Haemophilus influenza* have been estimated to account for 30% to 50% of cases of ON, whereas *N gonorrhea* accounts for less than 1% of cases of ON in the developed world. In the United States, perinatal transmission occurs in 30% to 40% of patients with maternal cervical infection. (2) Intrauterine transmission is also possible after the rupture of membranes.

Gonococcal infection in neonates born by cesarean delivery is rare. The first case of gonococcal conjunctivitis after cesarean delivery was described by Thompson et al in a case series of 7 patients in 1974. (3)

A variety of mechanisms have been proposed to explain the transmission of gonococcal infection in newborns born via cesarean delivery, as discussed. (4) One of the suggested modes of transmission is spread of infection from the infected birth canal to the amniotic fluid during a period between rupture of membranes and birth of the neonate. It is also possible to have postnatal transmission of infection from maternal genitalia to neonatal eyes by person-to-person transmission. (4) In another study, Handsfield et al found neonatal orogastric contamination with *N gonorrhoeae*, suggesting intrauterine infection. (5)

Prophylaxis

Historically, the introduction of postnatal prophylaxis with 2% silver nitrate decreased the incidence of neonatal gonococcal conjunctivitis from 10% to 0.3%. (1) A need for prophylaxis is under debate because of the decreasing incidence of STIs, effective treatment for conjunctivitis, and risk of developing resistance to antibiotic agents. Currently, the standard of care in the United States is the use of topical erythromycin ointment for prophylaxis. However, although the use of postnatal prophylaxis decreases the incidence of transmission, it does not completely eliminate it. (1)

Microbiology and Pathogenesis

Neisseria gonorrhoeae is an intracellular gram-negative diplococci. The outer membrane of *N gonorrhoeae* contains lipooligosaccharide, phospholipid, and a variety of proteins, including the porin (PorB) protein. PorB is essential for bacterial viability because it mediates ion exchange between *N gonorrhoeae* and the environment. PorB has also

TABLE. Causes of ophthalmia neonatorum

| • CHEMICAL | • VIRAL |
|------------------------------|------------------------|
| • Bacterial | • Adenovirus |
| • Chlamydia trachomatis | • Herpes simplex virus |
| • Neisseria gonorrhoeae | |
| • Haemophilus species | |
| • Streptococcus pneumoniae | |
| • Staphylococcus aureus | |
| • Staphylococcus epidermidis | |
| • Streptococcus viridans | |
| • Escherichia coli | |
| • Pseudomonas aeruginosa | |
| • Other | |

been implicated in being crucial for the pathogen to evade both the innate and adaptive immune systems. There are 2 alleles for PorB, known as PIA and PIB, that are associated with different phenotypes. The PIA strains are associated with disseminated disease because these strains are resistant to the bactericidal effects of human serum, and the PIB strains are associated with localized urogenital infections. (6)(7)(8) Initial attachment of gonococci to the surface of columnar epithelial cells is mediated by type IV pili. After attaching to mucosal cells, gonococci are engulfed in a process known as parasite-directed endocytosis, and the gonococci proceed to replicating intracellularly. The bacteria can then extend through lymphatics or can cause bacteremia, leading to disseminated disease.

Clinical Features

Infection usually is manifested 2 to 5 days after birth. It causes purulent conjunctivitis, with profuse exudate and swelling of the eyelids. If untreated, severe complications such as corneal scarring, blindness, and septicemia can occur.

Diagnosis

Gonococcal conjunctivitis is diagnosed by prenatal and perinatal history, physical examination, and microbiologic examination of conjunctival exudate. A Gram-stain of the conjunctival exudate should be examined for the presence of typical gram-negative intracellular kidney bean-shaped diplococci. For identifying *N gonorrhoeae* from nongenital sites, culture is the most widely used test. The patient should also be evaluated for chlamydia trachomatis, congenital syphilis, and HIV infections because of an increased incidence of coinfections with these pathogens. The mother's hepatitis B status should also be investigated. In addition, the patient's mother and her sexual partner should be evaluated for gonococcal and other STIs. (9)

Treatment

Infants suspected of having gonococcal ophthalmic disease should be hospitalized and observed for response to therapy and for disseminated disease (sepsis, arthritis, meningitis). After obtaining cultures (from eye, blood, urine, and CSF), empirical treatment should be started in patients in whom organisms are seen on Gram-stain or in those with negative Gram-stain but who are considered to be at high risk (eg, a mother with no prenatal care, history of STIs, or substance abuse). The current guidelines recommend treatment of neonatal gonococcal conjunctivitis

with a single dose of ceftriaxone 25 to 50 mg/kg, with a maximum of 125 mg given intravenously or intramuscularly. (9) Furthermore, patients require frequent irrigation of the eye with saline until resolution of discharge from the affected eye. (9) Topical antimicrobial therapy alone is not adequate to treat gonococcal conjunctivitis. Treatment of ON should be continued beyond the single treatment dose until all bacterial cultures are negative and systemic infection has been excluded, typically after 48 to 72 hours of therapy.

Lessons for the Clinician

- Clinicians should have a high index of suspicion for serious bacterial infections, such as infections with *Neisseria gonorrhoeae*, as the cause of neonatal conjunctivitis even in neonates born via cesarean delivery.
- Clinicians should start with systemic antibiotic drug treatment when gonococcal conjunctivitis is suspected.
- One should closely monitor neonates for ophthalmologic and systemic complications of gonococcal conjunctivitis.
- All newborns should be provided topical antibiotic drug prophylaxis at birth.

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Case 1: Eye Discharge in a 10-day-old Neonate Born by Cesarean Delivery

Gagandeep Singh, Alvaro Galvis and Samrat Das

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Case 1: Eye Discharge in a 10-day-old Neonate Born by Cesarean Delivery

Gagandeep Singh, Alvaro Galvis and Samrat Das

Pediatrics in Review 2018;39;210

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2 Fatigue and Shortness of Breath in an 18-year-old Girl

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AUTHOR DISCLOSURE Drs Lee and Miller have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An 18-year-old girl with a history of primary hypothyroidism presents for scheduled follow-up of her hypothyroidism. She has a history of significant mood disorder and psychiatric hospitalizations, and she has been living in a supervised group home for the past several years. She reports a 1-year history of neck swelling and states that she always feels tired at school. She states that she stopped taking her levothyroxine 6 months ago but without explanation and that she does not feel any different since stopping her medication. Her vital signs and examination findings are normal; her thyroid gland is not enlarged. Laboratory values are notable for a highly elevated thyrotropin level of 215.8 IU/L and a low free thyroxine level of 0.30 ng/dL (3.86 pmol/L). She is instructed to resume taking levothyroxine and is provided with an updated prescription.

She returns for a follow-up visit 3 months later. She completed 1 month of treatment with levothyroxine but has not refilled her prescription since then. The group home staff member states that they offer medication reminders to residents but that medication compliance is not mandatory. The patient reports onset of constipation, increasing fatigue, cold intolerance, sad mood, and shortness of breath with exertion. On further questioning, she reports that she feels light-headed and for the past week has had substernal chest pain that is worse with exertion.

Physical examination reveals an obese, alert, interactive adolescent. Her heart rate is 123 beats/min and her blood pressure is 114/56 mm Hg. She has bounding carotid pulses bilaterally. There is no thyromegaly or pretibial edema. Laboratory tests are performed, and after the results are received she is referred to the emergency department for further evaluation and management.

DISCUSSION

Her laboratory values from her office encounter demonstrate severe microcytic, microchromic anemia, with a hemoglobin level of 2.5 g/dL (25 g/L), a hematocrit level of 10.2%, a mean corpuscular volume of 72 μm^3 (72 fL), and a mean corpuscular hemoglobin concentration of 24.8 g/dL (248 g/L). She presents to the emergency department, where her complete blood cell count is rechecked and confirms severe anemia. Her white blood cell count and platelet count were

normal. Her thyroid studies are remarkable for an extremely elevated thyrotropin level of 393.40 IU/L and an undetectable free thyroxine level.

Hematology is consulted, and further hematologic and iron studies are obtained to identify the cause of her anemia. Our patient has a reticulocyte count of 1.91%, which is inappropriately normal for her degree of anemia. Iron studies show a normal total iron binding capacity of 423 $\mu\text{g/dL}$ (75.7 $\mu\text{mol/L}$), a normal transferrin level of 296 mg/dL (36.4 $\mu\text{mol/L}$), a low iron saturation of 9%, and a low ferritin level of 3.4 ng/mL (7.64 pmol/L).

Our patient receives 2 U of packed red blood cells in the emergency department. Because of her complaint of chest pain, an electrocardiogram (ECG) is performed, which shows sinus tachycardia with T-wave inversions and 1-mm ST-depressions in leads I, II, and aVF and T-wave inversions in leads V4 to V6. Serial serum troponin measurements are obtained and remain negative. Her ECG findings improve after the blood transfusions.

Our patient's anemia is determined to be most likely secondary to poorly controlled hypothyroidism. Levothyroxine therapy is restarted at her previous dose, and she receives an additional 2 U of packed red blood cells for her severe anemia, resulting in an increase in hemoglobin level to 7.9 g/dL (79 g/L) before discharge.

On outpatient follow-up several months later, she reports that she lost her medication shortly after hospital discharge and did not refill her prescription for levothyroxine. She reports generally not feeling well but denies dizziness, cold intolerance, constipation, or fatigue. Laboratory tests are performed, she is restarted on levothyroxine, and she is given strong encouragement to improve adherence to this treatment. Results of her laboratory testing are notable for a thyrotropin level of 112.6 IU/L, a free thyroxine level of 0.40 ng/dL (5.15 pmol/L), and a hemoglobin level of 4.9 g/dL (49 g/L). Outpatient social work is engaged to coordinate disease management with her group home supervisor, primary care physician, and psychiatrist. She subsequently leaves custody of social services and moves out of her group home. Attempts to compel her to return for follow-up care are unsuccessful.

THE CONDITION

Primary hypothyroidism is relatively common, seen in approximately 1% to 2% of adolescents, and is most often caused by autoimmune (Hashimoto) thyroiditis. Hypothyroidism occurs more frequently in females (2:1), and is more common in type 1 diabetes mellitus, Down syndrome, and Turner syndrome. (1) Adequate treatment with

levothyroxine normalizes thyroxine and thyrotropin levels and results in good outcomes if diagnosed in a timely manner. Symptoms of untreated hypothyroidism can be variable and include linear growth failure, constipation, fatigue, cold intolerance, and excessive weight gain.

Normocytic anemia is thought to occur in approximately one-third of individuals presenting with hypothyroidism. (2) Some studies suggest that up to 65% of children and adolescents with hypothyroidism may have concomitant anemia. (3) There are multiple mechanisms that may be involved in the development of anemia in untreated or undertreated hypothyroidism.

Erythropoietin production in the kidneys is dependent, in part, on adequate thyroid hormone levels. Thyroxine increases erythropoietin gene expression, thus increasing erythropoietin production. With less thyroid hormone circulating in the hypothyroid state, there is decreased plasma concentration of erythropoietin. Anemia secondary to hypothyroidism is usually normocytic and responds appropriately to thyroid replacement therapy. (4)

The microcytic anemia observed in our patient may also be secondary to iron malabsorption in the gut due to hypothyroidism. Low circulating thyroxine levels lead to decreased iron absorption and decreased iron incorporation into erythrocytes and may affect erythroid progenitor proliferation and differentiation. (5)(6) Hypothyroidism can also induce microcytic anemia via menorrhagia; however, it is unlikely that this contributed to our patient's anemia given her use of contraception with medroxyprogesterone acetate.

Although hypothyroidism is typically associated with normocytic anemia, our patient presented with a microcytic hypochromic anemia with an inappropriately normal reticulocyte count. We speculate that her long-standing hypothyroidism caused anemia due to iron deficiency as well as direct effects on erythropoietin production and proliferation of erythroid progenitors. Adequately addressing her anemia may require both adequate thyroxine replacement and iron replacement.

Our patient also presented with chest pain and several abnormal ECG findings that may have not all been related to her anemia. Severe, long-standing hypothyroidism can lead to pericardial effusions and nonpitting edema. This patient's echocardiogram noted a small to moderate circumferential pericardial effusion without hemodynamic significance. Because thyroxine therapy reverses all the cardiovascular changes associated with hypothyroidism, it would be of value to repeat an echocardiogram in the future to see whether this effusion resolves after improved compliance with levothyroxine therapy.

Although we suspect that the patient's anemia was caused by her hypothyroidism, this cannot be confirmed until her hypothyroidism is adequately treated. Although microcytic anemia is commonly found in patients with hypothyroidism, this case illustrates that in cases of prolonged untreated hypothyroidism, the degree of anemia can be severe.

Unfortunately the patient has continued to be poorly compliant with levothyroxine treatment, and despite multiple attempts to recall the patient, she has not returned for treatment of her hypothyroidism and severe anemia. Adolescent patients may respond to a diagnosis of chronic disease with anger, sadness, and denial. Our patient has additional psychosocial stressors, including her mood disorder and residence in a group home, which can increase the risk of withdrawal from active management of her disease. In this case, despite engaging social work and court-appointed guardians to support the patient's medical treatment, we were unable to improve her adherence to medical treatment of her hypothyroidism and anemia. It remains important to identify patients at risk for poor engagement in medical care and to use

support systems at the earliest opportunity to optimize outcomes.

Lessons for the Clinician

- Anemia is a common finding in patients with hypothyroidism. There is significant overlap in symptoms of hypothyroidism and anemia (cold intolerance, fatigue, depressed mood), and the clinician should be aware of findings of both anemia and hypothyroidism in patients with concerning symptoms.
- Adequate treatment of hypothyroidism is expected to result in resolution of normocytic anemia. Treatment of microcytic anemia in a patient with long-standing hypothyroidism may also require the addition of iron supplementation.
- Engagement of the adolescent patient in the management of a chronic disease can be a challenge, particularly if other psychosocial stressors are present. Early utilization of support services such as psychology and social work may be helpful in ensuring better compliance and follow-up.

References for this article are at <http://pedsinreview.aappublications.org/content/39/12/614>.

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Case 2: Fatigue and Shortness of Breath in an 18-year-old Girl

Jessica Lee and Ryan S. Miller
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Case 2: Fatigue and Shortness of Breath in an 18-year-old Girl

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2 Fever, Neck Pain, and Back Pain in a 16-year-old Boy

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AUTHOR DISCLOSURE Drs Trauernicht, Bharill, Panko, and Friehling have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy 16-year-old boy presents to the emergency department with 1 day of headache, neck pain, and fever. Three nights previously after soccer practice he had acute, severe low back pain, now resolved. He has otherwise been well, without nausea, vomiting, or vision changes. His immunizations are up to date. He has no known sick contacts. He does not take medications. He recently went camping but does not recall any insect bites.

Physical examination reveals an uncomfortable boy lying very still. His temperature is 100.9°F (38.3°C), heart rate is 91 beats/min, respiratory rate is 18 breaths/min, and blood pressure is 113/60 mm Hg. He has optic disc edema and limited range of motion of the neck with pain that radiates down his spine on flexion. The remainder of his physical examination findings are normal.

Laboratory evaluation reveals a normal complete blood cell count, basic metabolic panel, sedimentation rate, and urinalysis results. His C-reactive protein level is elevated at 3.85 mg/dL (38.5 mg/L). Findings from computed tomography of the head are normal. A lumbar puncture is obtained. Cerebrospinal fluid (CSF) is grossly bloody and xanthochromic, with 2,683 white blood cells/ μ L ($\times 10^9/L$) (85% neutrophils, 5% lymphocytes, 10% monocytes), 28,624 red blood cells (RBCs)/ μ L ($\times 10^9/L$), a low glucose level of 24 mg/dL (1.33 mmol/L), and an elevated protein level of 130 g/dL (1,300 g/L).

The patient is started on antibiotic therapy. His neck pain and fever resolve, but his low back pain returns and persists. The diagnosis is made after further evaluation.

DISCUSSION

This boy's presentation with fever and meningismus was highly concerning for bacterial meningitis. A CSF pleocytosis with neutrophilic predominance and hypoglycorrhachia (low glucose content in the CSF) supported this diagnosis. The elevated RBC count in the CSF was attributed to a traumatic tap. However, the patient continued to have low back, buttock, and bilateral posterior lower

extremity pain. Subsequent physical examination demonstrated intact strength in bilateral lower extremities but significant discomfort with flexion at the waist and with bilateral straight-leg raise. This prompted us to perform magnetic resonance imaging (MRI) of the lumbar spine, which revealed an intraspinal mass on the cauda equina extending to the conus medullaris, most consistent with a hemorrhagic myxopapillary ependymoma.

The Condition

Spinal cord and cauda equina neoplasms account for 3% of all primary brain and central nervous system tumors in pediatric and adolescent patients, and of those, ependymomas are the most common at 22%. (1) Conversely, of primary childhood ependymomas, only 13% are located in the spinal cord. (2) Myxopapillary ependymomas have a slight male predominance and more often occur in white adolescent males. (3) Myxopapillary ependymomas usually involve the filum terminale, cauda equina, or conus medullaris, although they can have thoracic involvement and can present with leptomeningeal disseminated disease. (3) Relapse and later onset of leptomeningeal disseminated disease are common.

Diagnosis

Back pain in children and adolescents is usually due to a musculoskeletal etiology. As was the case for our patient, a heightened suspicion for pathologic etiologies of back pain should occur when a child or adolescent endorses back pain that is persistent, severe, of a radicular distribution, or worse at night. In patients who are ultimately diagnosed as having myxopapillary ependymoma of the spinal cord, motor, sensory, sphincter, urinary, or gait abnormalities may occur. However, the absence of these symptoms does not rule out the possibility of a spinal cord tumor. Back pain initially can be subacute or nonspecific until compression of the spinal cord occurs, as these tumors are slow growing and are usually well circumscribed. An MRI of the brain and spinal cord is required for initial tumor staging.

Patients with myxopapillary ependymoma of the spinal cord may also present with signs of meningeal irritation, elevated intracranial pressure, and papilledema. If CSF analysis is pursued, it can reveal elevated protein and RBC values, xanthochromia, and hypoglycorrhachia. (4) Cytology is often negative, as was seen in our patient. These results may be confused with meningitis if imaging is not obtained first. Due to the low diagnostic yield of CSF analysis, lumbar puncture is not recommended unless central nervous system dissemination is suspected.

Management

No published therapeutic guidelines exist for treatment of spinal cord ependymoma in children due to a paucity of long-term outcome data. (5) The outcome in children generally depends on the grade and extent of tumor involvement in the spinal cord, which determines whether gross total resection (GTR) is possible. The GTR yields the best long-term survival with the lowest incidence of tumor recurrence. Survival in patients who underwent GTR is 97% at 5 years and 95% at 10 years based on some pediatric studies. (5) In comparison, pediatric patients who underwent subtotal resection plus radiation therapy had 5-year overall survival of 91%. (5)

The role of adjunctive radiotherapy after GTR is unclear. Some studies have demonstrated potential impact in recurrence-free survival rates given that the recurrence of local and metastatic disease is higher in children than in adults with myxopapillary ependymoma. (1) If only subtotal resection can be achieved due to tumor complexity and adherence to the spinal cord, there are 2 options: adjuvant radiotherapy or watchful waiting with close surveillance for tumor recurrence. Chemotherapy is not used in initial treatment of myxopapillary ependymoma.

The preferred method of postoperative surveillance for all patients is local MRI. (2) Our patient will be monitored with a lumbar spine MRI every 3 to 4 months for the first 2 years, every 6 months for 3 to 5 years, and yearly thereafter.

Patient Course

Our patient underwent successful GTR and had no evidence of residual or recurrent tumor on surveillance MRIs 3 and 6 months later. He described left lower extremity paresthesia in the immediate postoperative period but has intact strength and sensation on examination. He has not received any adjuvant chemotherapy or radiation.

Lessons for the Clinician

- Persistent, severe back pain in a healthy adolescent is not normal and requires evaluation.
- Although cerebrospinal fluid pleocytosis is most commonly due to meningitis, inflammatory and oncologic processes should be included in the differential diagnosis, particularly when the clinical presentation is atypical.
- Motor, sensory, sphincter, urinary, or gait abnormalities should not be considered essential to diagnosis of a spinal cord ependymoma.

References for this article are at <http://pedsinreview.aappublications.org/content/39/9/468>.



3 Fever, Vomiting, and Altered Mental Status in a 17-year-old Boy

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AUTHOR DISCLOSURE Drs Pelletier and Bartlett have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 17-year-old boy with a history of restrictive eating disorder and orthostatic hypotension presents via emergency medical services from an eating disorder facility with 1 week of dizziness and confusion and 1 day of fever. He also reports months of daily first-morning, nonbloody, and nonbilious vomiting.

On presentation to the emergency department he is febrile (temperature, 102.9°F [39.4°C]), tachycardic (heart rate, 112 beats/min), and hypotensive (blood pressure, 91/46 mm Hg) and requires oxygen via nasal cannula. His weight is 114.2 lb (51.8 kg) (3rd percentile), height is 64.6 in (164 cm) (5th percentile), and BMI is 19.3 (15th percentile). General physical examination findings are normal.

Shortly after arrival, the patient develops a brief episode of upper extremity tonic extension, unresponsiveness, and desaturation. He recovers spontaneously without an apparent postictal period. Repeated neurologic examination reveals slowed but appropriate responses to questioning. Cranial nerves, strength, sensation, and reflexes are normal. Upper extremity coordination is normal, but he has right greater than left ataxia with heel-to-shin testing. The patient is unable to stand for gait and Romberg testing due to dizziness.

Laboratory tests before fluid therapy are remarkable for a serum sodium concentration of 149 mEq/L (149 mmol/L) (reference range, 135–145 mEq/L [135–145 mmol/L]), a serum chloride concentration of 118 mEq/L (118 mmol/L) (reference range, 96–108 mEq/L [96–108 mmol/L]), leukocytosis, and normocytic anemia. Urinalysis results are normal, with a urine specific gravity of 1.010. Chest imaging reveals multifocal consolidation concerning for aspiration pneumonia. The patient receives fluids and ceftriaxone. Laboratory studies after fluid therapy reveal worsened hypernatremia and persistently dilute urine. Further testing reveals the underlying diagnosis.

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/3/144>.

DISCUSSION

The patient underwent computed tomography of the brain followed by magnetic resonance imaging (MRI) of the brain and total spine, which showed multiple masses in the foramen of Monroe, pineal region, suprasellar region, cervical medullary junction, and left cerebellum (Fig). Serum and urine osmolality confirmed diabetes insipidus, attributed to loss of pituitary function. Serum cortisol and adrenocorticotrophic hormone levels were inappropriately low. Thyrotropin and free thyroxine levels were also low. He was diagnosed as having panhypopituitarism and was managed with vasopressin, hydrocortisone, levothyroxine (after hydrocortisone replacement), and antibiotics. Serum tumor marker levels, including α -fetoprotein (AFP) and human chorionic gonadotropin (HCG), were normal. A lumbar puncture was performed, revealing normal cell counts, cytologic findings, and AFP levels and a minimally elevated HCG level (13 IU/L). Given the combination of multiple midline tumors, panhypopituitarism, and nearly normal tumor markers, the diagnosis of primary central nervous system (CNS) germinoma was suspected. The patient underwent brain biopsy, which confirmed the diagnosis.

Differential Diagnosis

Vomiting is a common complaint among children. The differential diagnosis of vomiting is exceptionally broad and includes etiologies from nearly every organ system.

Red flags for intracranial causes of vomiting include 1) first-morning symptoms, 2) positional vomiting, 3) vomiting without nausea, 4) altered mental status, 5) abnormal findings on neurologic examination, 6) seizures, and 7) blood pressure changes out of proportion to illness. (1)

The combination of fever, vomiting, and altered mental status in pediatrics should prompt the clinician to immediately rule out life-threatening etiologies. Such causes include encephalitis, stroke, seizures, CNS abscess or hemorrhage, intoxication or withdrawal, sepsis, electrolyte disturbances, malignancy, uremia, thyroid storm, and CNS vasculitis. Primary CNS tumors represent a small minority of such presentations. (1)(2)

The Condition

Germinomas are a subset of intracranial germ cell tumors, which represent approximately 3% of pediatric CNS tumors. They are related to other nongerminomatous germ cell CNS tumors (NGGCTs), including choriocarcinomas and teratomas. (2)(3)(4)(5) Most patients are 10 to 21 years old at diagnosis, and there is a 3:1 male to female predominance. (2)(3)(4)(5) Tumors are typically found in the midsagittal plane; the most common locations are the pineal gland and the suprasellar area. Other locations, such as the foramen of Monroe and the cerebellum, seen in our patient, are less common. (2)(3)(4)(5)

Presentation is variable depending on the tumor location. Tumors in the suprasellar region interrupt axonal projections from the hypothalamus to the pituitary gland and result in

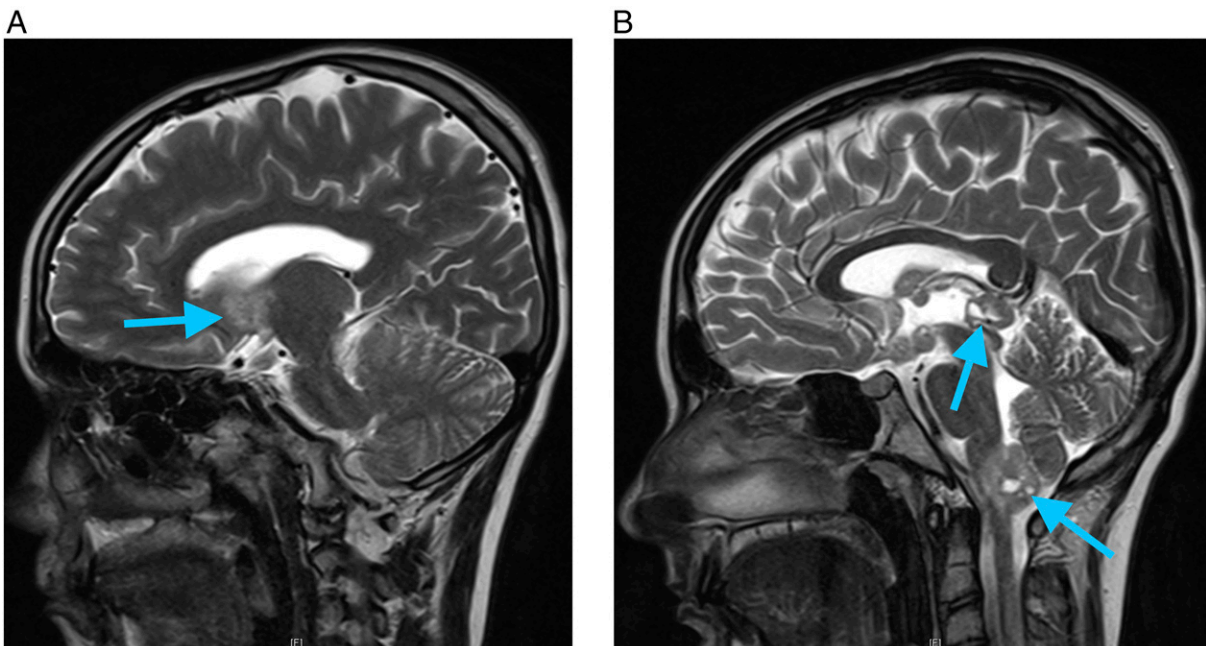


Figure. Sagittal T2-weighted magnetic resonance images show enhancing masses marked by arrows in the (A) suprasellar area, (B) pineal region, and the (B) cervical medullary junction. The patient also had a small left cerebellar mass and a tumor in the foramen of Monroe (not shown). The radiologic differential for multiple midline tumors in a patient this age included pinealoblastoma or germ cell tumor with ependymal spread.

endocrinopathies. Diabetes insipidus is the most common, but larger tumors can present with panhypopituitarism. (2)(3)(4)(5) Tumors in the pineal gland compress the aqueduct of Sylvius and can lead to obstructive hydrocephalus. Delayed diagnosis is common, especially in patients initially presenting with endocrine symptoms. (2)(3)(4)(5)

Diagnosis

The diagnosis can be suspected based on neuroimaging studies compatible with midline tumors in the characteristic locations, as described previously herein. Tumor markers, including AFP and HCG, are typically nearly normal in germinomas and are often drastically elevated in NGGCTs. Brain biopsy is required for definitive diagnosis. (2)(3)(4)(5) As with other patients with clinical panhypopituitarism, stabilization with hormone replacement is essential. (6) Hydrocortisone should be administered before diagnostic procedures or thyroid hormone replacement to avoid precipitating an adrenal crisis. (6)(7)(8)

Treatment and Prognosis

Patients should undergo MRI of the brain and spine and diagnostic lumbar puncture at the time of diagnosis for staging purposes. Patients with more than 1 site of tumor, positive CSF cytologic findings, or tumors outside of the CNS are considered to have metastatic disease. Germinomas are exquisitely radiosensitive. (9)(10)(11) Patients with metastatic disease universally receive craniospinal radiotherapy; those with localized disease may undergo local radiotherapy. Neoadjuvant chemotherapy with bleomycin, etoposide, and cisplatin or carboplatin may be used. (9)(10)(11) Survival is excellent, with 98% 5-year event-free survival among patients with metastatic germinoma. (12) However, patients receiving craniospinal radiotherapy are at increased risk for a variety of late complications, including vascular disease, stroke, endocrinopathies, and neurocognitive deficits. (13)

Case Follow-up

After treatment for his panhypopituitarism, the patient had a marked improvement in his nausea and vomiting, and his appetite dramatically improved. He gained 17.6 lb (8 kg) during the following 2 weeks, restoring his BMI to the 40th percentile. He began craniospinal radiotherapy and is followed by the oncology and endocrinology services. As of his last clinic visit, he was doing well, endorsing only fatigue. His nausea, vomiting, and orthostasis had completely resolved. Evaluation by pediatric psychiatry revealed that although he endorsed some anxiety around body shape, he denied dieting, calorie counting, or fear of weight gain, and he did not meet the criteria for a restrictive eating disorder.

Lessons for the Clinician

- Red flags for intracranial causes of vomiting include 1) first-morning symptoms, 2) positional vomiting, 3) vomiting without nausea, 4) altered mental status, 5) abnormal findings on neurologic examination, 6) seizures, and 7) blood pressure changes out of proportion to illness.
- Patients with diabetes insipidus often experience delayed diagnosis, and a high index of suspicion must be maintained. The condition can be suspected based on the low specific gravity of routine urinalysis combined with hypernatremia on serum chemical analysis.
- Primary central nervous system germinomas are a rare cause of panhypopituitarism and obstructive hydrocephalus, most commonly in adolescent boys. Brain biopsy is essential in diagnosis. Radiotherapy is the mainstay of treatment, and the prognosis is excellent.

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Case 3: Fever, Vomiting, and Altered Mental Status in a 17-year-old Boy

Jonathan Pelletier and Kathleen Bartlett

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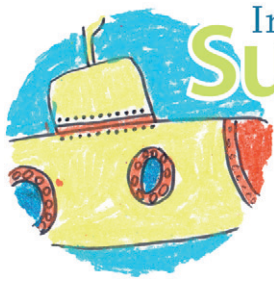
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2 Headache and Behavior Changes in an 11-year-old Boy

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AUTHOR DISCLOSURE Drs Mills, Yock, and King have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An 11-year-old previously healthy boy presents with 2 days of eye pain, headache, slowed speech, and word-finding difficulty. One day before presentation he attended school and football practice without any noted behavior change, trauma, confusion, or coordination difficulty. On the day of presentation, he awoke with left-sided headache and decreased appetite. He appeared “dazed” and unable to answer basic questions and was brought to the emergency department. He had no fevers or recent illness. He had exposure to outside farm cats, mosquitoes, and stream water, but no exposure to lakes or swimming pools. He has no known history of tick exposure or ill contacts.

On physical examination, the patient is afebrile (99.7°F [37.6°C]) and appears uncomfortable. His heart rate is 80 beats/min; respiratory rate, 18 breaths/min; blood pressure, 108/55 mm Hg; and oxygen saturation, 98% in room air. When asked what time it is, he responds by asking an unrelated question (“How tall is it?”). His speech pattern is normal. There are no cranial nerve deficits or clonus observed. Slight pain is elicited with forward neck flexion. His balance and gait are intact, and his strength is equal bilaterally. Sharp optic disc margins are noted. Cardiorespiratory examination findings are normal, and no heart murmur is appreciated. Oral examination findings are normal. No cutaneous lesions are noted. He is hospitalized for further evaluation of acute mental status change and left temporal headache. Additional history and imaging studies help establish the diagnosis.

The Case Discussion and Suggested Readings appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/2/93>.

DISCUSSION

Admission laboratory evaluation revealed a normal complete blood cell count and complete metabolic panel and normal levels of C-reactive protein, ammonia, and lactate. Findings from a drug screen and head computed tomographic scan were normal. A cerebrospinal fluid analysis revealed clear fluid with 6 white blood cells and unremarkable protein and glucose levels. An array of infectious disease tests were ordered on cerebrospinal fluid and serum.

On the second full hospital day the patient developed a fever (102.7°F [39.3°C]), worsening headache, and vomiting. Additional history was obtained revealing a recent dental abscess and tooth extraction 2 weeks before the onset of symptoms. He did not require prophylactic antibiotics before the procedure given his unremarkable medical history. Brain magnetic resonance imaging revealed multiple tiny foci of cortical and medullary enhancement of the bilateral cerebral hemispheres. An echocardiogram revealed a small mobile attachment on the left ventricular surface of the aortic valve with aortic regurgitation consistent with vegetation. The echocardiogram otherwise showed normal cardiac anatomy. The patient was diagnosed as having septic embolic encephalitis secondary to infectious endocarditis (IE).

The patient was subsequently transferred to the PICU due to progressive encephalopathy, difficulty waking, and the need for close neurologic monitoring. All laboratory results were normal except for a LaCrosse encephalitis immunoglobulin (Ig) G (IgM negative), which was attributed to a past exposure. Serial blood cultures were negative. Metronidazole was added for additional oral flora coverage given the history of dental procedure and blood culture obtained after initiation of antibiotic therapy. By the ninth hospital day, the patient's cognition had returned to near normal. A peripherally inserted central catheter was placed, and the patient was discharged from the hospital on an extended course of meropenem for presumed culture-negative endocarditis. Follow-up echocardiography 6 weeks after hospitalization demonstrated resolution of aortic regurgitation and vegetation. The cause of IE in our patient was consistent with bacterial seeding after a dental procedure involving gingival manipulation given his otherwise unremarkable medical history and normal cardiac anatomy.

The Condition

Infectious endocarditis, defined as an infection of the endocardium most commonly from a bacterial or fungal source,

is a rare condition in children. Most IE cases occur in patients with known repaired or unrepaired congenital heart disease (CHD), and IE in structurally normal hearts accounts for 5% to 13% of cases. Other risk factors for IE include history of rheumatic heart disease, prosthetic valves, history of endocarditis, and hospital device-associated bacteremia. In patients with structurally normal hearts, a history of prematurity and a central indwelling catheter have been found to increase the risk of developing IE. Bacteremia secondary to dental instrumentation is thought to be a rare cause of IE in children. The most common pathogens of IE in both patients with CHD and structurally normal hearts are *Staphylococcus aureus* and *Streptococcus viridans*, yet a variety of gram-negative bacteria account for the remaining cases of bacterial IE. In approximately 5% to 10% of patients with IE the bacterial cultures are negative.

Morbidity and mortality due to secondary complications such as mycotic aneurysm, abscess formation, and septic emboli may affect up to 30% of patients with IE. Septic embolic encephalitis is characterized by an acute, fluctuating delusional state. Other neurologic complications include cerebral artery occlusion resulting in ischemia or hemorrhage, infection of the cerebral parenchyma or meninges resulting in microabscesses, and arterial wall infection, which may lead to mycotic aneurysm and subsequent hemorrhage. Clinical symptoms vary widely and depend on the location, size, and number of septic emboli. Patients with end-organ dysfunction such as neurologic involvement may require close ICU monitoring.

Differential Diagnosis

The initial differential diagnosis in children presenting with altered mental status include viral and bacterial encephalitis, postinfectious encephalitis (ie, acute disseminated encephalomyelitis), autoimmune encephalopathy, or atypical migraine headache. Other etiologies, including trauma, tumor, ingestion, seizure, and vascular events, should be considered. In our patient, initial evaluation was most concerning for a viral infectious etiology, yet his turbulent illness course, development of fever, and positive history of aortic valve vegetation in the setting of a recent dental procedure raised red flags for a septic embolic event secondary to IE.

Management

Treatment of IE involves the management of acute secondary complications, prompt initiation of empirical antibiotics, and possible surgical intervention. Prompt initiation of antibiotic therapy significantly reduces the

risk of further endocardial damage and subsequent thromboembolic events. Empirical antibiotic therapy involves coverage of *S aureus* and *S viridans*, with subsequent tailoring to blood culture speciation. It is recommended that 3 or more blood cultures be obtained to aid in pathogen identification. Antibiotic courses are typically 4 to 6 weeks. Surgical intervention may be indicated for removal of vegetation or replacement of damaged cardiac valves. Given the complex nature of IE, a multidisciplinary approach is recommended, including consultation with infectious disease, cardiology, cardiovascular surgery, and/or neurosurgery. A 2007 guideline from the American Heart Association recommends antibiotic prophylaxis for dental procedures that involve oral mucosa perforation or gingival manipulation only in the following high-risk patients: CHD, prosthetic cardiac valve, unrepaired cyanotic CHD (including palliative shunts and conduits), repaired CHD with residual defect at the site of prosthetic material, previous IE, cardiac transplant with subsequent development of cardiac valvulopathy, and completely repaired cardiac defect with prosthetic material during the first 6 months after repair.

Lessons for the Clinician

- Given the prevalence of non-cardiac disease-associated endocarditis, consider risk factors such as prematurity, history of indwelling catheters, and recent skin and soft tissue infections as potential inciting events.
- When evaluating a patient with encephalopathy, clinicians should reassess the history and physical examination and broaden the differential diagnosis when the most common infectious disease, neurology, or rheumatology causes are not apparent on evaluation or the patient fails to fit the expected clinical course.
- Antibiotic prophylaxis for dental procedures involving manipulation of the gingiva or oral mucosa perforation is recommended only in patients at high risk for infectious endocarditis.

Suggested Readings

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Case 2: Headache and Behavior Changes in an 11-year-old Boy

David Mills, Lindsey C. Yock and Erin King

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5 Headache, Vomiting, and Elevated Blood Pressure while Voiding in an 8-year-old Girl

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AUTHOR DISCLOSURE Drs Healey, Fardy, and Chan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An 8-year-old girl from South Sudan presents to the emergency department with a history of severe headache and vomiting with urination. She describes the headache as being present “all over” her head and rates the pain “15/10.” There is no history of morning or positional headache. She has had a history of vomiting with urination and defecation since she was 1 year old. From 1 to 6 years of age, the vomiting occurred sporadically, but during the 2 years before the emergency department visit, vomiting was occurring 4 to 5 times daily with voiding and defecation.

Initial vital signs reveal a heart rate of 114 beats/min, a respiratory rate of 24 breaths/min, a temperature of 97.0°F (36.1°C), and blood pressure (BP) of 122/88 mm Hg. Funduscopic examination results are normal. Results of cardiovascular, respiratory, abdominal, and central nervous system examinations are normal.

In the emergency department, we observe the child screaming with a headache and vomiting after 3 separate voids. Her BP increases to 143/94 mm Hg during these episodes. Between voids, she does not complain of headache and does not vomit. Her headache is treated with intravenous morphine. After treatment with morphine, the BP returns to 120/84 mm Hg. We provide no further treatment for hypertension in the emergency department. She is hospitalized. Further review of the history and testing lead to the diagnosis.

The Case Discussion appears with the online version of this article at <http://pedsinreview.aappublications.org/content/39/3/147>.

DISCUSSION

The review of medical records from previous clinic visits showed that she had been consistently hypertensive during the previous 2 years, with BPs ranging from 105/65 to 126/70 mm Hg (for her height and age, 50th percentile BP is 99/59 mm Hg, stage 1 hypertension is 116/77–123/84 mm Hg, and stage 2 hypertension is >123/84 mm Hg). Her elevated BPs were not observed on multiple clinic visits. She has no history of excessive sweating but did complain of occasional palpitations in the 6 months before presentation to the emergency department.

The initial differential diagnosis included brain tumor, essential hypertension, benign intracranial hypertension, and pheochromocytoma.

On laboratory evaluation, the complete blood cell count; blood urea nitrogen, creatinine, electrolyte, glucose, thyrotropin, and morning cortisol levels; and urinalysis results were all normal. Findings from a computed tomographic (CT) scan of the head were also normal. Abdominal ultrasonography revealed the presence of a bladder mass (Fig 1). Abdominal magnetic resonance imaging confirmed the presence of a lobulated, heterogeneous, well-defined lesion measuring $3.9 \times 3.1 \times 3.3$ cm in the superior aspect of the bladder (Fig 2). Studies on a 24-hour collected urine sample showed a significantly elevated norepinephrine level of 77.5 pg/ml (13,111,600 pmol/L; reference range, 0.93–4.68 pg/ml). Her plasma norepinephrine level was also elevated at 0.130 pg/ml (22,000 pmol/L; reference range, <0.005 pg/ml). Based on the clinical and biochemical picture, a diagnosis of bladder paraganglioma was made.

The patient was referred to the surgical team for resection of the paraganglioma. She was prepared for surgery initially with phenoxybenzamine, with atenolol added after adequate α -blockade was achieved. With a 3-week period of treatment, her BP normalized to 106/58 mm Hg. She then underwent transvesical resection of the tumor, with partial resection of the bladder cuff. Her BP remained normal after surgery. One month after surgery, the patient had a normal BP and no recurrence of symptoms.

Results of the genetic studies for both von Hippel-Lindau (VHL) and succinate dehydrogenase (SDH) gene mutations were negative.

The Condition

Paragangliomas are neuroendocrine tumors that arise from neural crest-derived cells or organs. They develop along the sympathetic and parasympathetic ganglia, particularly the carotid body, jugular foramen, mediastinum, organ of Zückerkandl, and periaortic region. These tumors are rare, with an incidence of less than 0.3 cases per million per year. Between 10% and 20% of cases are diagnosed in the pediatric population. Overall, paragangliomas account for 1% of pediatric patients with hypertension.

Most paragangliomas are hormonally active, producing excessive amounts of catecholamines that are responsible for the symptoms seen in many patients at the time of diagnosis (Table). Bladder paragangliomas may present with hematuria or paroxysmal symptoms during voiding in 50% of patients due to involvement of the detrusor muscle.



Figure 1. Abdominal ultrasonography shows a mass in the urinary bladder.



Figure 2. Abdominal magnetic resonance imaging shows the presence of a lobulated, heterogeneous, well-defined lesion measuring 3.9 × 3.1 × 3.3 cm in the superior aspect of the bladder.

The first step in the diagnosis of a paraganglioma is to confirm excessive catecholamine production by measurement of plasma or urine levels. Measurement of fractionated plasma metanephrine levels has sensitivity near 100% but specificity of 85%. The sample must be collected while the patient is supine because false-positive results may occur in the sitting position. A 24-hour urinary metanephrine test has

sensitivity of 88% and specificity of 99.7%. Collection is time-consuming, and urine must be collected during a crisis or immediately afterward. A CT scan or a magnetic resonance image is then used to localize the tumor(s). Functional imaging, including metaiodobenzylguanidine or positron emission tomography, is highly specific and can confirm the catecholamine-secreting nature of the tumor. It also can be used to localize tumors not seen with cross-sectional imaging and identify other sites of disease.

Surgical resection is the definitive treatment for a paraganglioma. Before surgery, it is crucial to achieve adequate α_1 -adrenergic blockade with an agent such as phenoxymethamine to minimize intraoperative BP elevation due to catecholamine surges that may occur due to surgical manipulation of the tumor. Once adequate α -blockade is obtained, a β -blocker may be added to prevent reflex tachycardia. If β -blockade is added too early, a hypertensive crisis can result from significant unopposed α -mediated vasoconstriction. Medical preparation for surgery may take several weeks. In addition, the patient should be salt-loaded a few days before surgery to expand blood volume and minimize postoperative hypotension.

Between 40% and 59% of childhood paragangliomas are due to genetic mutations, including *VHL*, *SDH*, neurofibromatosis 1 (*NF1*), and rearranged during transfection (*RET*) proto-oncogene germline mutations. Consultation with a geneticist to arrange genetic testing is, therefore, recommended for all children presenting with paragangliomas. Approximately 12% of pediatric paragangliomas are malignant. Risk factors for malignancy include extra-adrenal location, size greater than 6 cm, and sporadic occurrence.

The prognosis for a surgically resected paraganglioma is excellent if the lesion is benign. However, these tumors can sometimes have unpredictable clinical behavior and metastasize late in the clinical course, and, therefore, long-term follow-up with measurement of plasma or urine metanephrine levels and imaging studies is required.

Lessons for the Clinician

- Vomiting and headaches may be the presenting symptoms for elevated blood pressure in children.
- Catecholamine-secreting tumors should be considered in the differential diagnosis of hypertension in children.
- Symptoms of catecholamine excess may occur only during micturition if the tumor is located in the bladder.
- Plasma metanephrine level is the test of choice to confirm catecholamine excess.
- Children with paragangliomas should undergo testing for underlying mutations in the *VHL* or *SDH* genes.

TABLE. Signs and Symptoms of Paraganglioma in Children

| CLASSIC | NONSPECIFIC |
|-------------------------|---------------------------|
| Hypertension | Blurred vision |
| Paroxysmal episodes | Hyperglycemia |
| • Headache | Gastrointestinal symptoms |
| • Palpitations | Weight loss |
| • Diaphoresis | Polyuria |
| Pallor | Polydipsia |
| Orthostatic hypotension | Low-grade fever |
| Syncope | Behavioral changes |
| Tremor | |
| Anxiety | |

Case 5: Headache, Vomiting, and Elevated Blood Pressure while Voiding in an 8-year-old Girl

Ara Healey, Liam Fardy and Kevin Chan

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2

Headaches with Recurrent Rash and Mucosal Ulcerations

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AUTHOR DISCLOSURE Drs Robertson and Ohta have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An 18-year-old male from the Netherlands presents to the general pediatric clinic for follow-up from 2 visits to the emergency department (ED) with an approximate 1-week history of daily debilitating left-sided frontoparietotemporal headaches with associated intermittent photophobia, phonophobia, left-sided weakness, paresthesia, gait instability, bilateral hand tremors, and blurry vision. The headaches are exacerbated in intensity when supine and waking him from sleep. He denies associated nausea, vomiting, or abdominal pain. Onset occurred after his first presentation to the ED for recurrent oral aphthous stomatitis and erythema multiforme-like lesions. The headaches were poorly responsive to non-steroidal anti-inflammatory drugs and acetaminophen; however, they would improve slightly with intravenous fluids, diphenhydramine, and prochlorperazine. Results of laboratory evaluation, including a urine drug screen and salicylate and alcohol levels, are normal. Results of noncontrast head computed tomography and magnetic resonance imaging are also reassuring.

His medical history was significant for depression, anxiety, polysubstance abuse, and herpes simplex virus-1 in addition to the recurrent oral aphthous stomatitis and erythema multiforme-like lesions. His aphthous stomatitis had been severe enough to require hospital admission 3 times in the past. During his first admission 4 years earlier, he had esophageal and genitourinary tract involvement in addition to the erythema multiforme-like lesions. Extensive evaluation by multiple specialists at that time did not reveal a unifying diagnosis. His second 2 admissions were in close proximity, within 12 months of his clinic presentation. He again had extensive aphthous stomatitis, erythema multiforme-like rash, and a small genital ulceration. A mouth lesion was biopsied and revealed a nonspecific autoimmune inflammatory process and no evidence of herpes infection.

His growth curve shows an approximate 5-kg weight loss over a 1-year period, with a BMI of 17.55 on the day of presentation. On physical examination he has a few scabbed, curvilinear papular lesions inferior to the bilateral periorbital regions. During the examination he develops a headache, becomes diaphoretic with bilateral hand tremor, and complains of photophobia and blurred vision. Review of previous records and expert consultation confirms the suspected clinical diagnosis.

DISCUSSION

The constellation of recurrent oral and genitourinary ulcerations, erythema multiforme–like lesions, and new-onset headaches with neurologic manifestations in the setting of otherwise unexplained weight loss suggested a clinical diagnosis of Behçet disease.

The Condition

Behçet disease is an autoimmune vasculitis that indiscriminately affects both arteries and veins of all sizes. (1) It is classically known to occur primarily along the “Silk Road,” that is, the countries of Eastern Asia to the Mediterranean, Turkey being the most common (80–370 cases per 100,000 population). (2) Behçet disease is much less common in Northern European and North American populations. Specifically, countries of interest in this case include the Netherlands (prevalence of approximately 1 per 100,000) and the United States (0.33 per 100,000). (3) Young men are typically more severely affected than young women. Although the etiology of this disease is not yet fully understood, it is commonly associated with HLA-B51 (approximately 60% of affected patients) and can tend to cluster in families, although it does not have a known autosomal inheritance pattern. (4) It is postulated that multiple other genetic and environmental factors play a role in the manifestation of Behçet disease in an otherwise susceptible individual.

Behçet disease has the potential to affect any organ; however, it tends to primarily affect skin and mucous membranes. The classic triad is oral and genital ulcerations with uveitis, as originally described by Turkish dermatologist Dr Hulusi Behçet in 1937. (4) Approximately 97% of affected individuals have the classic oral ulceration, and 60% to 90% have recurrent genital ulcerations. Oral ulcerations can range from herpetiform (1–3 mm) to major (>10 mm). The genital ulcerations can involve any part of the genitourinary tract and commonly involve the scrotum in males and vulva in females. (1)

Dermatologic manifestations include papulonodular lesions, erythema nodosum–like lesions, acneiform rashes, pseudofolliculitis, pyoderma gangrenosum, and, less commonly, erythema multiforme–like rashes. (1) Individuals can exhibit a positive pathergy test result, which consists of an exaggerated, localized cutaneous reaction (such as papules, pustules, or ulceration) as a result of puncture from a sterile needle. This result is positive in only approximately 15% of Korean, 30% of British, and 60% of Turkish patients. This is also commonly seen in other neutrophilic dermatoses, such as Sweet syndrome or pyoderma gangrenosum, as well as other autoimmune inflammatory conditions, such

as inflammatory bowel disease (IBD). (5) Our patient did not exhibit a positive reaction to pathergy testing in the office.

Behçet disease can also involve the gastrointestinal tract, strongly mimicking IBD and making it nearly indistinguishable. Biopsy of the patient’s oral ulcerations from previous admissions showed an acute on chronic autoimmune process, composed predominantly of lymphocytic and neutrophilic infiltration, without evidence of granulomatous formation. Endoscopy and colonoscopy did not demonstrate evidence of acute colitis, although during 1 admission he did demonstrate esophageal ulcerations. Results of a fecal calprotectin test were negative.

Neurologic involvement can be a particularly serious complication, although it occurs in less than 10% of patients. (6) Individuals will typically present with either parenchymal or nonparenchymal involvement (ie, meningoencephalitis versus vascular complications, including cerebral venous thrombosis). Although headaches do not denote specific neurologic involvement as a direct result of the disease process itself, they are a common comorbidity and include predominantly tension headaches as well as migraine headaches. (6) As noted previously, results of magnetic resonance imaging performed in the ED were otherwise normal. Given the concern for potential vascular involvement due to the presence of headaches with other neurologic manifestations, magnetic resonance angiography/magnetic resonance venography was attempted; however, due to patient anxiety it was not able to be completed despite anxiolysis.

Along with neurologic involvement, a devastating feature of classic Behçet disease is ocular involvement, which can be particularly severe in males. It can manifest in forms of anterior/posterior uveitis, retinal vasculitis, scleritis, episcleritis, and thrombosis of retinal arteries and veins. Patients can often demonstrate ocular pain, visual disturbance/loss, and photophobia. Despite our patient’s complaints of blurred vision and ocular pain, the results of an ophthalmologic evaluation were normal. (1)

Diagnostic Criteria

The 2 predominant clinical scoring systems for establishing a diagnosis of Behçet disease are the International Study Group (ISG) criteria from 1990 (Table 1) (7) and the International Criteria for Behçet’s Disease (ICBD) from 2006 (Table 2). The ISG criteria are slightly more specific (96.0% vs 90.5%); however, the ICBD criteria are significantly more sensitive (94.8% vs 85.0%). (8)

Our patient met the criteria for both the ISG and ICBD scoring systems with recurrent oral ulcerations, recurrent genital ulcerations, and skin lesions consisting of both

TABLE 1. ISG Criteria for the Diagnosis of Behçet Disease (7)

Must have:

Recurrent oral ulceration—minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient that recurred ≥ 3 times in one 12-mo period

Plus ≥ 2 of the following:

Recurrent genital ulceration—aphthous or scarring observed by physician or patient

Eye lesions—anterior uveitis, posterior uveitis OR cells in vitreous on slit lamp examination OR retinal vasculitis observed by ophthalmologist

Skin lesions—erythema nodosum observed by physician or patient, pseudofolliculitis, papulopustular lesions OR acneiform nodules observed by physician in postadolescent patients not taking corticosteroids

Positive pathergy test—read by physician at 24–48 h

ISG=International Study Group.

erythema multiforme–like lesions and papulopustular lesions associated with exacerbations.

Differential Diagnosis

Given that Behçet disease can affect any organ, there are many other conditions that it mimics, and ultimately it is a diagnosis of exclusion. Systemic inflammatory conditions such as

systemic lupus erythematosus, IBD, and celiac disease should be considered and ruled out. Adverse drug reactions should be taken into consideration. Sexually transmitted infections such as human immunodeficiency virus, herpes simplex virus-1/2, gonorrhea/chlamydia, and syphilis are potential confounders. Other conditions, such as cyclical neutropenia, vitamin deficiencies (B_{12} in particular), and Sweet syndrome, need to also be considered. In our patient, during previous hospital admissions, these conditions were taken into consideration, and extensive multidisciplinary evaluation effectively ruled these diagnoses out; however, the clinical diagnosis of Behçet disease was never given.

Management

Immunosuppression is the mainstay of treatment. Acutely, this can be accomplished with both topical and systemic corticosteroids. Antibiotics (such as doxycycline) in a mouthwash form for oral mucosal ulcerations can reduce the bacterial load contributing to exacerbation and prolongation of healing. Pain control with topical or systemic analgesics is important during acute exacerbations, particularly when there is difficulty eating as a result of pain. Under the guidance of a rheumatologist, disease-modifying drugs such as azathioprine, mycophenolate mofetil, methotrexate, and tacrolimus can be used to provide more extensive immunosuppression and better control of the disease. Consideration of adverse effects of such drugs and appropriate monitoring are key to proper management. (1)

Patient Course

After consultation with pediatric rheumatology, he was started on azathioprine 100 mg/d and was increased to 150 mg/d within a few weeks. His symptoms dramatically improved over 2 to 3 months, and he was symptom free and regained the previously lost weight by 6 months from the start of treatment. He had no further relapses within 18 months and was then lost to follow-up due to relocation.

Lessons for the Clinician

- The clinician should be able to recognize the classic clinical pattern and be suspicious for Behçet disease, particularly the hallmark presentation of recurrent oral and genital aphthosis with other systemic manifestations.
- The clinician should recognize the differential diagnosis for Behçet disease and consider the diagnosis to be one of exclusion, ruling out more common etiologies such as sexually transmitted diseases, systemic inflammatory conditions (eg, inflammatory bowel disease, systemic

TABLE 2. ICBG International Criteria for the Diagnosis of Behçet Disease (2006) (8)

| SIGNS/SYMPTOMS | POINTS |
|---|--------|
| Ocular lesions | 2 |
| Genital aphthosis | 2 |
| Oral aphthosis | 2 |
| Skin lesions | 1 |
| Neurologic manifestations | 1 |
| Vascular manifestations | 1 |
| Positive pathergy test results ^a | 1 |

A total score greater than 4 is positive. ICBG=International Criteria for Behçet Disease.

^aPathergy test is not required in the primary scoring system, although, if conducted, an extra point may be assigned for a positive result.

lupus erythematosus), Sweet syndrome, celiac disease, cyclical neutropenia, and vitamin deficiencies.

- The clinician should recognize the need for advanced imaging in the setting of neurologic signs/symptoms with a clinical suspicion of Behçet disease. In addition to magnetic resonance imaging, magnetic resonance angiography/magnetic resonance venography should be performed to help determine vascular involvement versus parenchymal involvement.
- The clinician should recognize the need for multidisciplinary evaluation of individuals suspected of having Behçet disease. This will include referrals to rheumatology and ophthalmology, and may include gastroenterology, neurology, urology, and/or dermatology based on symptoms.

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1 Hematemesis in a 30-month-old Boy

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EDITOR'S NOTE

We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: <https://mc.manuscriptcentral.com/pir>.

AUTHOR DISCLOSURE Drs Damodharan and Danko have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 30-month-old boy with no significant medical history presents to the emergency department with a single unprovoked episode of hematemesis. The mother describes the emesis as bright red blood. This has never occurred before, and after the episode the patient was drinking milk with no noticeable pain or irritation. The mother reports that for a few days preceding the hematemesis the patient's solid intake decreased, but he continued to take in liquids without difficulty and had no weight loss. She also noted dark maroon-colored stools for about the past week. He is not taking any medications and is otherwise healthy.

Vital signs are all within normal limits for his age. On physical examination, the patient appears pale but has no abdominal tenderness, hepatomegaly, splenomegaly, lesions in the oropharynx, or petechiae and bruising on the skin.

A complete blood cell count is obtained and is significant for a hemoglobin level of 10.6 g/dL (106 g/L), which is down from 12.0 g/dL (120 g/L) from a lead screening a few weeks earlier. A stool guaiac sample is also obtained and is positive.

The decision is made to admit the patient to the pediatric gastroenterology service for further endoscopic evaluation. On admission, the patient continues to have multiple blood-tinged emesis episodes and refuses to take in solids. During these episodes, his vital signs remain within normal limits and he continues to tolerate oral intake of fluids.

He is made nothing per os overnight and is taken for esophagogastroduodenoscopy in the morning for presumptive upper gastrointestinal (GI) bleed given his history of hematemesis and melena. Endoscopic evaluation reveals a bleeding Dieulafoy lesion in the proximal gastric body (Fig 1). The mucosa surrounding the lesion is injected with epinephrine to provide hemostasis, and the vessel is then electrocoagulated with a bipolar probe (Fig 2). The patient tolerates the procedure well.

The next day the patient has 1 more episode of coffee ground emesis, but a repeated complete blood cell count shows a hemoglobin level increase to 11.2 g/dL (112 g/L). He is discharged after tolerating his normal diet with no more episodes of vomiting.

DISCUSSION

The Condition

Dieulafoy lesions are an uncommon cause of GI bleeds in not only the pediatric population but in adults as well. The term refers to a large tortuous artery in the submucosal layer that erodes to the surface. The lesion usually occurs in the proximal stomach, but it can be found in the small bowel, colon, and esophagus.

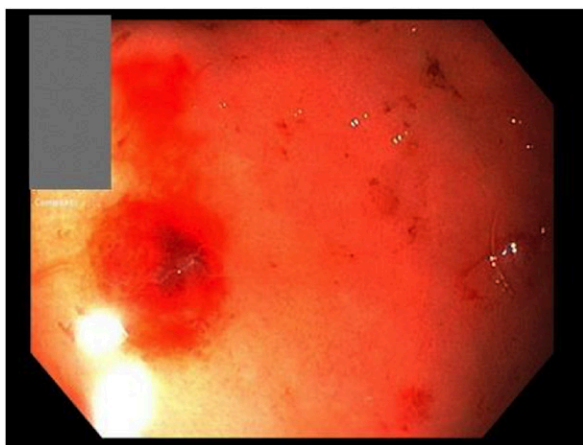


Figure 1. Bleeding Dieulafoy lesion in the gastric body.

The etiology of the lesion is unclear, but it seems to be a histologically normal artery that fails to undergo normal branching as it traverses the GI wall. It is postulated that the relatively large pulsating vessel disrupts the epithelium and subsequently erodes, causing massive hemorrhage. The lesion does not cause symptoms until it bleeds, so its true incidence is unknown. However, these lesions are believed to account for 1% to 2% of all acute GI hemorrhages in adults. (1) Only a handful of case reports have shown Dieulafoy lesions in the pediatric population, with little information known of its incidence.

Differential Diagnosis

Upper GI bleeding typically presents with hematemesis, melena, and, in some patients, hematochezia. The differential diagnosis in our patient's age group primarily includes esophagitis, gastritis, peptic ulcer disease, Mallory-Weiss tears, esophageal varices, vascular malformations, and foreign bodies. The initial evaluation should be directed at assessment of the risk of circulatory compromise. After this, a thorough history and physical examination should be performed to narrow the differential diagnosis. A history of gastroesophageal reflux, repeated vomiting, and abdominal pain raises the suspicion of esophagitis, gastritis, peptic ulcer, or a Mallory-Weiss tear. A history of jaundice, or findings of splenomegaly or a firm nodular liver edge, suggests underlying liver disease and bleeding from esophageal varices secondary to portal hypertension. When considering liver cirrhosis, it is important to realize that the liver may be enlarged, shrunken, or normal in size depending on the stage of the disease. It is also important to consider extra-GI causes that can present as GI bleeds. For example, recurrent epistaxis may point to a nasopharyngeal source. Patients with thrombocytopenia or a coagulopathy would be at risk for bleeding from a preexisting lesion in the GI tract. A thorough drug history must be taken, including over-the-counter medications such as nonsteroidal

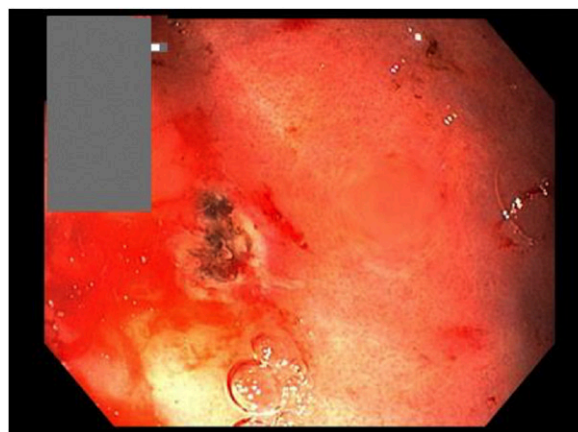


Figure 2. Dieulafoy lesion after obtaining endoscopic hemostasis.

anti-inflammatory drugs. The skin should also be examined for any evidence of vascular malformations that can be associated with GI vascular disorders. Initial laboratory evaluation may include a complete blood cell count with a differential count, a complete metabolic panel, and coagulation studies. Plain films can be obtained to look for evidence of bowel obstruction or foreign bodies, and ultrasonography can assess for liver disease. A nasogastric aspirate may also be helpful to confirm active gastric bleeding. However, the definitive test is endoscopy, which is both diagnostic and potentially therapeutic.

Treatment

The initial treatment of choice for most Dieulafoy lesions is endoscopic management. As in our patient, epinephrine is typically injected to achieve hemostasis, which is then followed by electrocoagulation. Other endoscopic therapies include sclerotherapy, hemostatic clipping of the ulcerated lesion, and band ligation. (2) Of note, patients diagnosed as having a Dieulafoy lesion are at risk for recurrent bleeds even after successful endoscopic treatment. For lesions that fail to respond to endoscopic management, angiography with embolization has been used as a second-line treatment, with surgery performed as a last option. (2)

Lessons for the Clinician

- Dieulafoy lesions are rare but should be considered in patients who present with signs of an upper gastrointestinal bleed.
- For patients who present with gastrointestinal bleeding in hemodynamic decline, stabilization and prompt endoscopic evaluation and therapy are indicated to prevent further deterioration.
- Patients typically recover quickly after successful treatment of a Dieulafoy lesion but should always be aware of the risk of a repeated bleed.

References for this article are at <http://pedsinreview.aappublications.org/content/39/11/560>.

Case 1: Hematemesis in a 30-month-old Boy

Sudarshawn Damodharan and Istvan Danko

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2 Hemolacria, Hematochezia, and Hematuria in an 11-month-old Boy

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PRESENTATION

AUTHOR DISCLOSURE Drs Manzano, Shantharam, Webb, Finelt, and Hengel have disclosed no financial relationships relevant to this article. Dr Manzano's current affiliation is Massachusetts General Hospital, Boston, MA. Dr Webb's current affiliation is Community Health Services, Hartford, CT. Dr Hengel's current affiliation is Maimonides Children's Hospital, Brooklyn, NY. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

A previously healthy 11-month-old boy born at full-term presents with a rash for 3 days. It began as a single purpuric lesion on his right ear and progressed over 2 days to involve his face (Fig 1) and all extremities. On the day of presentation, mom reports swelling of his face, hands, and feet; nasal congestion; cough; bilateral conjunctivitis; and "red tears." He has poor oral intake and urine output, worsening fussiness, is difficult to console, but has no tactile fever. Two weeks ago he completed 10 days of amoxicillin for acute otitis media. His medical, surgical, travel, allergic, and family histories are otherwise unremarkable. His vaccines are up to date. He takes no prescribed or over-the-counter medications.

On physical examination he is crying and appears uncomfortable. He is afebrile, and tachycardic to 158 beats/min with normal blood pressure and respiratory rate. He has innumerable 1- to 4-cm, violaceous, erythematous, nonblanching, and nonpruritic targetoid patches and plaques on his face and extremities (Figs 1–3), sparing his abdomen, palms, soles, back, and genitals. He has rhinorrhea, bilateral conjunctivitis, red-stained tears (hemolacria), erythematous tympanic membranes, and a targetoid patch on the hard palate. He has painful, nonpitting edema of his face, hands, feet, and scrotum, with intact cremasteric reflexes bilaterally. The remainder of his examination findings are normal.

The white blood cell count is normal, complete metabolic panel shows evidence of dehydration, urinalysis is significant for hematuria, and stool is occult blood positive. An oropharyngeal swab is positive for enterovirus/rhinovirus.

DISCUSSION

Hospital Course

The child was admitted to the inpatient unit for management of dehydration and further evaluation of the described rash. He became febrile during the admission and continued to have hemolacria, occult hematuria, and hematochezia for several days. Hemolacria was observed with and without conjunctivitis. On admission, scrotal edema was observed, and scrotal ultrasonography showed



Figure 1. Characteristic targetoid lesions present on the patient's left ear and face.

adequate blood flow and bilateral orchitis and epididymitis. There was low suspicion for significant renal disease given his normal levels of urine protein, creatinine, and urine output once rehydrated.

A dermatology consult was sought, and the patient was diagnosed as having acute hemorrhagic edema of infancy with extensive mucosal involvement. Supportive inpatient care was provided. He was discharged several days after admission after improvement of oral intake. The patient's rash and edema remained but were improving on discharge.

The Condition

Vasculitides are among the many etiologies responsible for the development of a rash in the pediatric population. Our patient presented with acute hemorrhagic edema of infancy (AHEI), a benign leukocytoclastic vasculitis that manifests with a dramatic rash despite a self-limited and benign course. The exact etiology of AHEI is unknown;



Figure 2. Characteristic targetoid lesions present on the patient's left arm.



Figure 3. Characteristic targetoid lesions present on the patient's right leg.

it is loosely associated with an infectious trigger and certain medications and immunizations. Upper respiratory tract infections or gastroenteritis, aspirin, acetaminophen, penicillin, erythromycin, cephalexin, over-the-counter cough syrup, and the diphtheria-pertussis-tetanus, conjugated *Haemophilus influenzae*, and measles-mumps-rubella vaccines are all roughly correlated with onset of AHEI.

The classic clinical triad in AHEI consists of fever, large purpuric skin lesions, and tender edema. It typically occurs in children aged 4 months to 3 years. Although AHEI is considered by some to be a variant of Henoch-Schönlein purpura (HSP), the characteristic rash and localization of the dermatologic manifestations of these vasculitides vary. In contrast to HSP, the AHEI rash typically manifests as multiple targetoid and purpuric lesions of varying sizes that primarily involve the face, ears, and extremities. The lesions in AHEI do not localize to dependent areas of the body like they do in HSP. Periorbital edema, orchitis, epididymitis, mucosal involvement, hematuria, and hematochezia have all been reported. To our knowledge, there are no previous reports of hemolacria displayed by a patient with AHEI.

Unlike HSP, AHEI does not commonly cause intussusception, renal disease, or other complications, although acute renal failure has been reported and is theoretically possible given the similarities to HSP. Proteinuria increases the concern for renal disease. Complete recovery is expected within 1 to 3 weeks after initial presentation, and recurrence is very rare.

A thorough patient history and identification of the clinical manifestations of AHEI are sufficient for diagnosis. Laboratory evaluations may show leukocytosis, an elevated erythrocyte sedimentation rate, thrombocytosis, and eosinophilia. Biopsies of the cutaneous lesions will show a

leukocytoclastic vasculitis. Immunofluorescence may display C3, C1q fibrinogen, or immunoglobulin depositions in the endothelium.

Differential Diagnosis

Other alternate diagnoses to consider include HSP, meningococemia, disseminated intravascular coagulopathy (DIC), Kawasaki disease, and serum sickness. Meningococemia and DIC secondary to sepsis should be considered when a purpuric rash is present in the context of an active infection. Disseminated intravascular coagulopathy is a consumptive process and, therefore, thrombocytopenia is expected. However, the patient's platelet count was within normal limits, thereby making DIC unlikely. The patient was afebrile by history, with a low-grade fever during hospitalization, and he was not toxic appearing as would be expected in a child with meningococemia. Despite edematous extremities and bilateral conjunctivitis, he did not fulfill the diagnostic criteria for Kawasaki disease. Although serum sickness is a reasonable diagnosis to consider in a child presenting with a rash 2 weeks after recent treatment with antibiotics, the characteristic targetoid and hemorrhagic appearance of his rash is more typical of AHEI.

Management

Conservative, symptomatic management is recommended when caring for a patient with AHEI. The efficacy of corticosteroids, antibiotics, and antihistamines is controversial, and further investigations are needed.

Lessons for the Clinician

- The clinical triad of acute hemorrhagic edema of infancy (AHEI) includes low-grade fever; palpable, nondependent, purpuric rash on the face, trunk, and extremities; and tender edema.
- Mucosal involvement can manifest as hemolacria, hematuria, hematochezia, conjunctivitis, oral lesions, and nasal congestion.
- Despite the acuity of onset and dramatic rash, AHEI is largely a benign, self-limiting condition that resolves in 1 to 3 weeks, warranting conservative symptomatic management.
- Renal disease is reported, and periodic urinalysis for several months, similar to what is done for Henoch-Schönlein purpura, is a reasonable approach to follow-up.

Suggested Readings for this article are at <http://pedsinreview.aappublications.org/content/39/8/418>.

Case 2: Hemolacria, Hematochezia, and Hematuria in an 11-month-old Boy
Giovanna Manzano, Rohini Shantharam, Elke Webb, Nika Finelt and Kyle Hengel
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1 Hemoptysis in a Healthy 13-year-old Boy

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EDITOR'S NOTE

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AUTHOR DISCLOSURE Drs Winningham and Estrellado-Cruz have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy 13-year-old boy presents with cough and hemoptysis of 1 week duration. His cough is nonproductive and he describes a small amount of hemoptysis every day. There is no history of fever, changes in appetite, weight loss, exercise intolerance, orthopnea, or chest pain. His mother does report that he has had occasional night sweats.

Vital signs at the time of hospital admission are as follows: temperature, 100.8°F (38.2°C); heart rate, 100 beats/min; blood pressure, 109/55 mm Hg; respiratory rate, 22 breaths/min; and oxygen saturation, 98% on room air. His weight is 76 lb (34.4 kg) (<1st percentile). Physical examination findings are normal.

Laboratory studies include the following: white blood cell count, 7,400/ μ L (7.40×10^9 /L); hemoglobin level, 7.9 g/dL (79 g/L); red blood cell count, 7.04×10^3 / μ L; mean corpuscular volume, 79.7 μ m³ (79.7 fL); reticulocyte count, 1.7% (0.017); platelet count, 420×10^3 / μ L (420×10^9 /L); and elevated inflammatory markers, with an erythrocyte sedimentation rate of 92 mm/hour and a C-reactive protein level of 4.9 mg/dL (49 mg/L). His serum electrolyte levels and liver function test results are normal.

His initial chest radiograph shows consolidation in the right upper lobe. Due to concern for tuberculosis (TB), quadruple anti-TB medications (rifampin, ethambutol, isoniazid, and pyrazinamide) are started on admission. Additional evaluation includes QuantiFERON-TB Gold (Qiagen, Hilden, Germany), sputum acid-fast bacillus stain and culture, aerobic respiratory culture, human immunodeficiency virus antibody screen, and histoplasma antibody and mycoplasma immunoglobulin (Ig) M and IgG antibody levels. Results of these tests are normal. Further imaging and subsequent laboratory testing lead to the diagnosis.

DISCUSSION

The differential diagnosis included an infectious process such as TB, infections with other mycobacterium, histoplasma, or mycoplasma versus an intrinsic lung injury such as a vasculitis, pulmonary hemosiderosis, or sarcoidosis. On hospital admission, a chest radiograph was performed that showed left upper lobe and right lower lobe lesions. The patient continued to have hemoptysis, and with the abnormal chest radiograph findings, a chest computed tomographic

scan was performed. Findings revealed mixed nodular and ground glass consolidation (Fig 1). Bronchoalveolar lavage was subsequently performed that revealed greater than 80% hemosiderin-laden macrophages. A complete rheumatologic evaluation revealed elevated antimitochondrial peroxidase (MPO) antibody level greater than 8.0 (normal is <0.4) and an indeterminate perinuclear antineutrophil cytoplasmic antibody (p-ANCA). Lung biopsy showed mild capillaritis (ie, inflammation of the capillary vessels) (Fig 2), and renal biopsy revealed proliferative glomerulonephritis with crescent formation (Fig 3). Clinicians concluded that his condition was most consistent with microscopic polyangiitis (MPA) based on a positive anti-MPO antibody, which strongly suggests ANCA-related vasculitis along with tissue biopsy findings. His anti-TB medications were eventually discontinued given a negative TB evaluation.

The Condition

The ANCA-associated vasculitides (AAV) are infrequent diagnoses in childhood. Microscopic polyangiitis is a systemic small-vessel vasculitis that is primarily manifested with findings of necrotizing glomerulonephritis and pulmonary capillaritis. The AAV are autoimmune diseases targeting either proteinase 3 or MPO. The incidence is approximately 1:100,000 in the general population. Males are more frequently affected than females, and the average age at onset is approximately 50 years. In children, the condition is rare and usually manifests at the beginning of the second decade of life.

Clinical Presentation

The main organs involved in AAV include the kidneys, lungs, joints, heart, peripheral nerves, skin, and central nervous system, clinically manifesting as myalgias, arthralgias, arthritis, purpura, abdominal pain, gastrointestinal tract bleeding, and peripheral neuropathy.

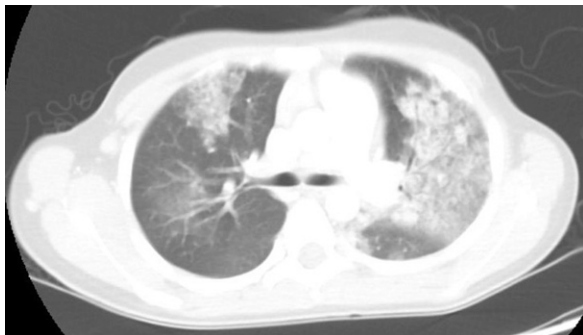


Figure 1. A chest computed tomographic scan shows mixed nodular and ground glass consolidations in both lungs.

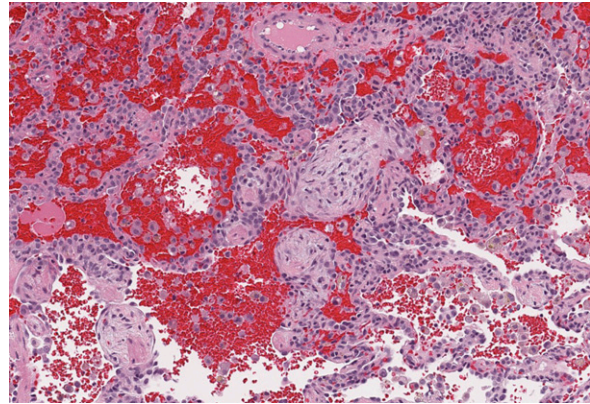


Figure 2. Lung biopsy shows evidence of mild capillaritis.

Pulmonary and renal complications are common in AAV. Renal involvement is characterized by a rapidly progressive glomerulonephritis. The most common manifestation of lung involvement in the anti-AAV is alveolar hemorrhage, which has a similar frequency of occurrence in children and adults. The pulmonary capillaritis is the direct cause of the manifestation of alveolar hemorrhage.

Lung involvement is an important contributory factor to morbidity and mortality. The diagnosis should be suspected in patients with hemoptysis, anemia, and diffuse alveolar infiltrates on chest radiography. Patients can present with chronic findings of isolated anemia, persistent cough, dyspnea on exertion, and recurrent radiologic infiltrates.

Etiology

Diffuse alveolar hemorrhage (DAH) syndromes occur as a result of injury to the small vessels in the pulmonary circulation; DAH is classified into 2 groups: 1) absence of pulmonary capillaritis or 2) presence of pulmonary capillaritis

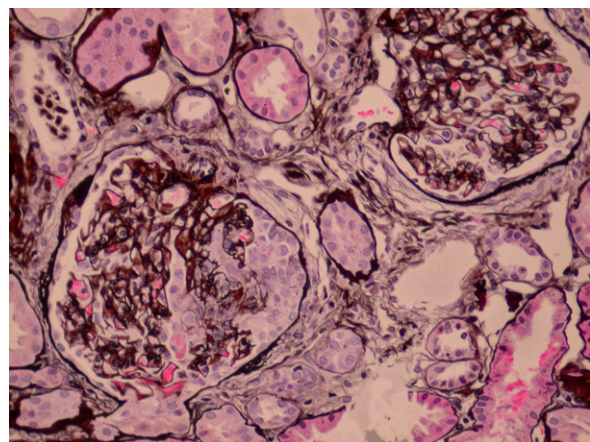


Figure 3. Renal biopsy shows proliferative glomerulonephritis with crescent formation.

(characterized by inflammatory disruption of alveolar interstitium).

Without capillaritis, DAH can be caused by cardiac disease (mitral stenosis, pulmonary veno-occlusive disease, arteriovenous malformation, pulmonary hypertension, pulmonary hemangiomatosis) and noncardiac pathology (idiopathic pulmonary hemosiderosis, bone marrow transplant, coagulation disorders, celiac disease, infanticide).

With pulmonary capillaritis, DAH is most commonly caused by autoimmune disorders, including Wegener granulomatosis, Goodpasture syndrome, MPA, systemic lupus erythematosus, antiphospholipid antibody syndrome, Henoch-Schönlein purpura, IgA nephropathy, polyarteritis nodosa, and drug-induced capillaritis.

Pathophysiology in MPA is based on autoantibodies, produced by B lymphocytes and plasma cells, activating a proinflammatory phenotype of neutrophils that cause necrotizing damage to vascular walls of small vessels, often involving the kidneys and lungs. The activated neutrophils release reactive oxygen species and lytic enzymes that damage and lyse endothelial cells. There may be an association of increased levels of autoantibodies preceding the onset of clinical relapse of AAV.

Diagnosis

A computed tomographic scan is recommended to confirm the diagnostic findings identified on chest radiography. Helpful markers in making the diagnosis of MPA are the presence of the p-ANCA and the MPO antibody. The ANCAs are found in most patients with MPA, and most of these are p-ANCA. Although ANCA is a valuable diagnostic tool, it is limited in monitoring disease activity and in predicting response to therapy. To look for evidence of vasculitis, it is often recommended to perform a biopsy of the involved tissue.

Management

When immunosuppression treatment such as cyclophosphamide (CYC) and high-dose glucocorticoids were introduced as management for AAV, 1-year mortality was reduced from 80% to 10% to 20%. However, malignancy and infertility are adverse effects of CYC. In terms of safety, rituximab (RTX) seems more favorable than CYC. In addition, studies have shown that in patients with AAV who have renal involvement, RTX and CYC yield identical remission rates. As a chimeric monoclonal antibody, RTX interrupts this antibody-mediated autoimmune disease by depleting precursors of ANCA-producing cells.

Because AAV are autoimmune, other organs should be evaluated and monitored for their function.

Patient Course

He was started on management with pulse corticosteroids and RTX, which resulted in a good clinical response, his renal function was stabilized, and inflammatory markers of p-ANCA and MPO titers improved. He had 1 pulmonary function test performed 2 months after discharge from the hospital that revealed normal spirometry and total lung capacity.

Pulmonary function test results have remained stable. He is continuing with maintenance therapy with RTX infusion for a total of 18 months, as well as prophylactic trimethoprim-sulfamethoxazole.

Lessons for the Clinician

- Microscopic polyangiitis is a rare disease in children, and without aggressive therapy it has a poor prognosis.
- The diagnosis should be suspected in patients with hemoptysis, anemia, and chest radiographic findings that reveal a diffuse alveolar infiltrate pattern.
- Patients can present with chronic findings of isolated anemia, persistent cough, dyspnea on exertion, and recurrent radiologic infiltrates.
- The relapse and mortality rates are reduced with cyclophosphamide and high-dose glucocorticoids.
- As an approved alternative for remission induction and because of its favorable adverse effect profile, rituximab is used more frequently to treat patients with relapsing or refractory disease.

ACKNOWLEDGMENT

The authors acknowledge the Children's Mercy Hospital Pathology Department for lung biopsy and renal biopsy slide.

Note. This case is based on a presentation by Drs Winningham and Estrellado-Cruz at the CHEST Conference: Montréal, Québec, Poster Session: Pulmonary Manifestations of Systemic Disease Student/Resident Case Report Posters I, Presentation Date: October 27, 2015, Poster Number: 3873.

An Abstract of this case is also published in the CHEST Journal as Microscopic Polyangiitis, a rare Pediatric Case. Estrellado W et al. CHEST, Volume 148, Issue 4, 877A.

Suggested Readings for this article are at <http://pedsinreview.aappublications.org/content/39/8/415>.

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Grace Winningham and Wendy Estrellado-Cruz

Pediatrics in Review 2018;39;415

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1 Hemoptysis, Hypoxia, and Anemia in a 10-year-old Girl

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EDITOR'S NOTE

We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: <https://mc.manuscriptcentral.com/pir>.

AUTHOR DISCLOSURE Drs Tarchichi and Lupo have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 10-year-old premenarchal girl with a history of chromosome 16 short arm duplication, seizures, and global developmental delay is transferred to us from another hospital for evaluation of new-onset severe anemia, hypoxia, and hemoptysis. At an outside hospital, her heart rate was 140 beats/min, blood pressure was 160/80 mm Hg, and oxygen saturation level was 88% on room air (100% on nonrebreather oxygen supplementation), and she was afebrile. There was no obvious bleeding source on examination. Laboratory evaluation revealed a hemoglobin level of 6.4 g/dL (64 g/L) compared with 13.2 g/dL (132 g/L) 3 years earlier. Chest radiography revealed bilateral diffuse infiltrates. She was transferred to our hospital.

On admission to our hospital, the patient's mother reports that the patient is acting more aggressive than usual and appears pale. Two weeks before admission she had a brief episode of mild upper respiratory tract symptoms without fever. The review of systems is otherwise negative, including no history of weight loss, hematochezia, black tarry stool, epistaxis, bruising/bleeding, scleral icterus, jaundice, or hematuria.

Vital signs on hospital admission are as follows: temperature, 98.8°F (37.1°C); heart rate, 98 to 137 beats/min; respiratory rate, 22 to 36 breaths/min; and blood pressure, 96 to 120/47 to 89 mm Hg. Her oxygen saturation level is 80% on room air and increases to 100% on 100% nonrebreather mask. She is not in distress and is nonverbal but follows commands (consistent with her baseline). Her conjunctivae are pale, and she has poor inspiratory effort without wheezes, rales, or rhonchi. The physical examination results are otherwise normal.

Laboratory studies, imaging, and bronchoalveolar lavage help with the diagnosis.

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/3/140>.

DISCUSSION

Our patient's laboratory studies revealed a hemoglobin level of 5.1 g/dL (51 g/L), a mean corpuscular volume of 62.2 fL, a serum iron level of 20 μ g/dL (3.6 μ mol/L), a total iron-binding capacity of 409 μ g/dL (73.2 μ mol/L), iron saturation of 5%, a transferrin level of 292 mg/dL (35.9 μ mol/L), a haptoglobin level less than 15 mg/dL (150 mg/L), a lactate dehydrogenase level of 416 U/L (6.9 μ kat/L), and a reticulocyte count of 2.6%. Stool guaiac test results were negative. Urinalysis did not show red blood cells, and the peripheral smear did not show evidence of hemolysis. Endoscopy and colonoscopy showed no signs of bleeding. Our patient's radiograph revealed patchy airspace opacities throughout both lungs, with no evidence of pneumothorax or pleural effusion (Fig 1). Bronchoalveolar lavage showed 270 white blood cells, 39,250 red blood cells, and hemosiderin-laden macrophages. Owing to concern for vasculitis or systemic illness, the patient underwent lung biopsy, and the lung grossly was found to be diffusely hemorrhagic and quite dark in color. The final pathologic diagnosis was idiopathic pulmonary hemosiderosis (IPH).

The Condition

Idiopathic pulmonary hemosiderosis is an uncommon cause of alveolar hemorrhage. (1)(2)(3) It is classically defined by hemoptysis, diffuse parenchymal infiltrates on chest radiography, and iron deficiency anemia. (1)(2)(4) The degree of anemia varies with the amount of hemorrhage, and the clinical presentation can be variable. The incidence is approximately 0.24 to 1.23 per million. The etiology of IPH is not fully understood. (1)(2) Many authors believe that IPH likely occurs in genetically predisposed individuals and is triggered by an event, such as an infection. (1)(5) *Stachybotrys* has been linked to a cluster of patients with IPH in Cleveland, but this association was not established. (1) Nuesslein et al (1) stated,

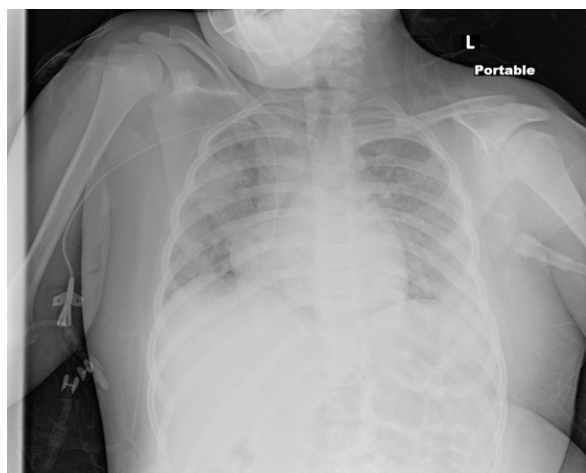


Figure 1. Chest radiograph shows airspace opacities in both lungs.

“When any bleeding occurs from alveolar capillaries into pulmonary tissue, hemoglobin will be transformed to hemosiderin. Hemosiderin is ingested by macrophages, which will then produce pro-inflammatory molecules leading to chronic inflammation and fibrosis if bleeding occurs repeatedly.” Idiopathic pulmonary hemosiderosis is more common in children than adults and typically occurs in children younger than 10 years (mean age, 4 years). (1)(2)(5) Historically, the median survival rate has been 3 to 5 years from the time of diagnosis. (4) Most experts now believe that early diagnosis and aggressive immunosuppression can significantly prolong survival. (1)(2)

Idiopathic pulmonary hemosiderosis has been associated with celiac disease, an autoimmune disorder. This association is known as the Lane-Hamilton syndrome, and there are numerous cases described in the literature. (6) (7) It is also reported that 1 of 4 children with IPH will develop an immune disorder later in life. (2) Conditions that can present similarly to IPH are Goodpasture syndrome and Heiner syndrome (primary hemosiderosis with cow milk hypersensitivity). (1) However, Goodpasture syndrome is associated with acute kidney injury usually associated with rapidly progressing glomerulonephritis in addition to the hematemesis, anemia, and pulmonary infiltrates. Heiner syndrome is associated with cow milk protein allergy.

Diagnosis

The variability in presentation can make diagnosis challenging. In their 1999 article “Prognosis in Pediatric Idiopathic Pulmonary Hemosiderosis,” Saeed et al (2) reported that “all patients diagnosed had anemia and pulmonary infiltrates, 85% had hypoxemia, 65% had hemoptysis, and 70% had fever.”

The chest radiograph pattern for IPH is classically described as a “butterfly” or “batwing” pattern, with symmetrical alveolar infiltrates slanting upward toward the lateral chest walls. (1)

When clinically suspected and after ruling out alternative causes of pulmonary hemorrhage, the diagnosis is typically made, with bronchoscopy and bronchoalveolar lavage revealing hemosiderin-laden macrophages. A lung biopsy is not required but can be used to rule out vasculitis or other systemic illness. (2)

Management

Initial treatment of acute IPH is oral prednisone/prednisolone (2 mg/kg per day) and is effective in most patients. High-dose corticosteroids for 6 months followed by long-term low-dose treatment may be beneficial for some patients. (1) If prednisolone is ineffective, second-line treatment is either pulse dose methylprednisolone (30 mg/kg daily for 3 days)

or cyclophosphamide (2–3 mg/kg per day). (1) Other immunosuppressive agents, such as azathioprine or chloroquine, have been shown to be beneficial in some patients. (1) These agents are typically added to corticosteroid therapy or used alone if there is a contraindication to corticosteroid treatment. In those who make a complete recovery, the corticosteroids may be tapered and stopped under close follow-up. Some patients require corticosteroid treatment for an indefinite period.

The clinical course of the disease is variable, and alveolar hemorrhage can be recurrent. When this occurs, the severity of pulmonary symptoms can range from blood-tinged sputum to severe and life-threatening hemorrhage requiring transfusion and intubation. If the hemorrhage interferes with airflow, rigid bronchoscopy may be necessary to remove clots. (1) The diffusing capacity of carbon monoxide is a sensitive and useful indicator for monitoring IPH treatment. (8) With treatment, the diffusing capacity of carbon monoxide should return to normal; therefore, elevations can be an indicator of continued or recurrent intrapulmonary hemorrhage. (8)(9)

Owing to a high clinical suspicion for IPH, our patient was started on corticosteroids and showed clinical improvement. After the diagnosis was confirmed on biopsy, the decision was made to continue oral prednisone indefinitely. She has had no recurrences, and her respiratory status remains stable.

Lessons for the Clinician

- Idiopathic pulmonary hemosiderosis classically presents as a clinical triad of diffuse pulmonary parenchymal infiltrates on chest radiography, iron deficiency anemia, and hemoptysis.
- Bronchoalveolar lavage positive for hemosiderin-laden macrophages is typically sufficient for diagnosis; however, in rare cases, lung biopsy may be required to rule out other systemic illness as the cause.
- Survival has significantly improved with timely diagnosis, treatment, and monitoring.

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4 Hypoglycemia after Nissen Fundoplication in a 7-month-old Girl

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AUTHOR DISCLOSURE Drs Krishnamurthy, Chandra, and Henwood-Finley have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 7-month-old girl underwent a Nissen fundoplication for severe gastroesophageal reflux. On postoperative day 5, she was found to be sweating profusely, and her hands and feet felt moist. Her blood glucose level at the time was 32 mg/dL (1.8 mmol/L). Serial measurements of blood glucose levels before and after meals over a 48-hour period demonstrated preprandial hypoglycemia (blood glucose level, 32 mg/dL [1.8 mmol/L]) and postprandial hyperglycemia (blood glucose level, 233 mg/dL [12.9 mmol/L]) (Fig 1). When hypoglycemia recurred, a critical sample was collected to rule out possible etiologies of hypoglycemia, including congenital hyperinsulinism, growth hormone deficiency, cortisol deficiency, fatty acid oxidation defects, organic acid disorders, and iatrogenic causes.

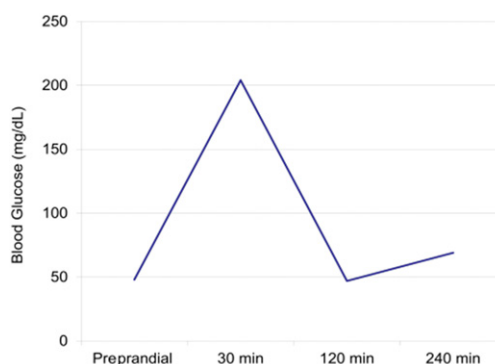


Figure 1. Preprandial and postprandial blood glucose levels.

The Case Discussion and Suggested Readings appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/1/40>.

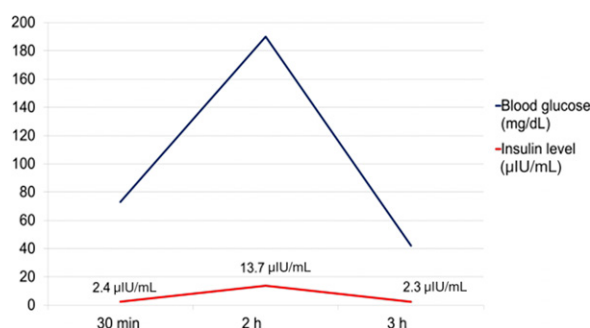


Figure 2. Diagnostic evaluation of dumping syndrome showing postprandial blood glucose and insulin levels.

DISCUSSION

Our patient's pattern of postprandial hyperglycemia followed by hypoglycemia suggested dumping syndrome. The diagnosis was confirmed by laboratory testing, which showed a rise in insulin levels from 2.4 $\mu\text{IU/mL}$ (16.7 pmol/L) at baseline to 13.7 $\mu\text{IU/mL}$ (95.2 pmol/L) 30 minutes after a feeding followed by a decline to 2.3 $\mu\text{IU/mL}$ (16.0 pmol/L) 90 minutes after a feeding while her postprandial glucose readings increased to 190 mg/dL (10.5 mmol/L) and then fell to 42 mg/dL (2.3 mmol/L) by the conclusion of the test (Fig 2). Acarbose is a medication that inhibits α -glucosidase in the intestinal brush border and is used in the treatment of type 2 diabetes in adults. It was started at an initial dose of 12.5 mg 3 times a day. Preprandial blood glucose levels improved to greater than 70 mg/dL (>3.9 mmol/L) 3 hours and sometimes 6 hours after feedings, but she continued to have readings less than 70 mg/dL (<3.9 mmol/L) after feedings not associated

with a dose of acarbose. The dose of acarbose was then increased to 25 mg 3 times a day. She maintained all blood glucose readings greater than 70 mg/dL (>3.9 mmol/L) and was discharged with this dose of acarbose (Fig 3).

Awareness of dumping syndrome as a possible complication after Nissen fundoplication helps facilitate rapid diagnosis and treatment.

The Condition

Dumping syndrome is a common complication of Nissen fundoplication, especially in pediatric patients. Dumping syndrome can be classified into 2 types: early (osmotic) and late (hypoglycemic) (Fig 4). Both types are associated with a large volume of gastric content entering the duodenum or jejunum, resulting in symptoms of dumping, including sweating, tachycardia, abdominal pain, nausea, and diarrhea. Moreover, the symptoms of dumping syndrome can be divided into vasomotor or gastrointestinal. Vasomotor symptoms include tachycardia, sweating, flushing, palpitations, and dizziness, and gastrointestinal symptoms include nausea, cramping, abdominal pain, and diarrhea.

Early or osmotic dumping occurs up to 45 minutes after a meal and results from passage of a large volume of osmotic material into the small bowel. This causes an influx of fluid from the intravascular space. There is a subsequent reduction in circulating volume, resulting in release of vasoactive peptides, including vasoactive intestinal peptide, causing the symptoms described previously herein.

Late or hypoglycemic dumping occurs 2 to 4 hours after a meal and is due to rapid delivery of glucose into the duodenum. Consequently, a rapid increase in serum glucose levels

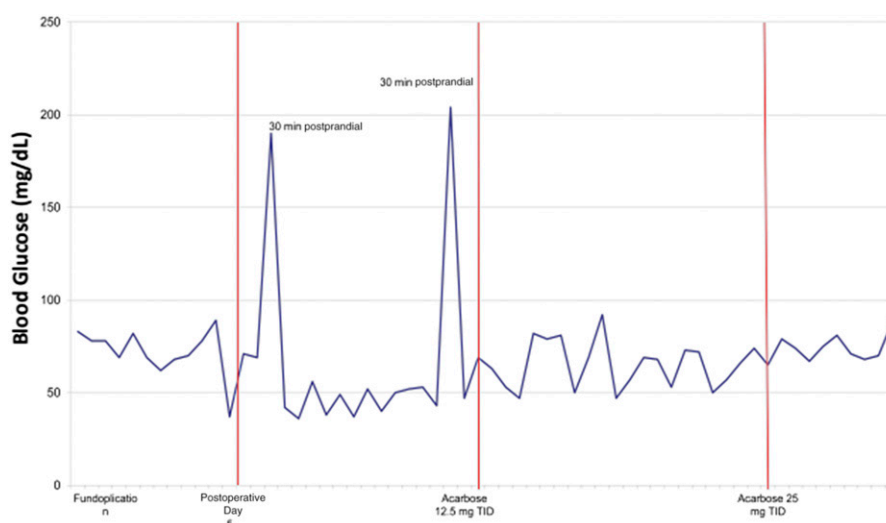


Figure 3. Blood glucose levels before and after intervention with acarbose. All blood glucose values are obtained immediately preprandial unless labeled otherwise.

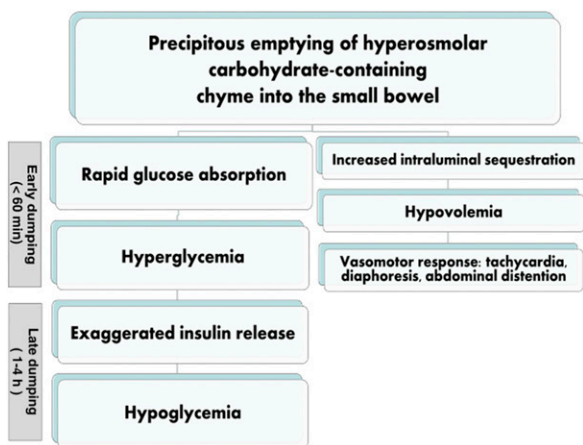


Figure 4. Pathophysiology of dumping syndrome.

results in excessive insulin secretion, leading to hypoglycemia. Symptoms of late dumping syndrome are much more subtle and nonspecific compared with those of early dumping syndrome. Confirmation of late dumping syndrome requires demonstration of hypoglycemia after an oral glucose tolerance test.

Clinical Presentation

Dumping syndrome is a common complication after gastric surgery in adults but is not as well described in infancy and childhood. There are relatively few case reports and studies describing dumping syndrome in children. This may be because children lack classic gastrointestinal symptoms of

early dumping and have severe postprandial hyperglycemia as a first sign, which often goes unrecognized.

Diagnosis

The first step to making a diagnosis of dumping syndrome is to obtain a detailed history. If the patient has had previous gastrointestinal surgery, such as a Nissen fundoplication, this may be a clue to the clinician that the patient may have dumping syndrome. Moreover, symptoms of hypoglycemia a few hours after a meal, such as sweating, tachycardia, and gastrointestinal symptoms, including bloating, abdominal cramping or pain, and diarrhea, should raise clinical suspicion for dumping syndrome.

Once dumping syndrome is on the list of differential diagnoses, it is important to obtain blood glucose and insulin levels every 30 minutes for 2 to 3 hours after feeding. This will help establish the pattern of postprandial hyperglycemia followed by hypoglycemia. An oral glucose tolerance test is helpful to provoke symptoms of early dumping syndrome and to evaluate for late reactive hypoglycemia. A decrease of more than 108 mg/dL (>6 mmol/L) between peak and nadir blood glucose measurements has been proposed as diagnostic criteria for dumping syndrome. Continuous glucose monitoring has also been used to clearly detect large glycemic fluctuations around times of feeding. This modality has been helpful in ensuring that treatment ameliorates rapid changes in glucose.

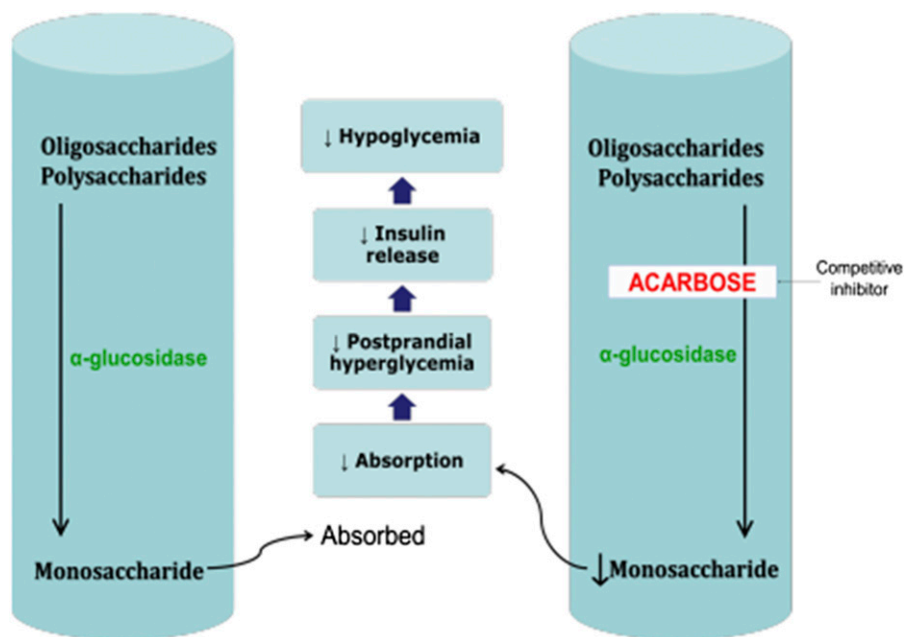


Figure 5. Mechanism of action of acarbose.

Management

Dietary modifications are the first step to inhibiting rapid gastric emptying. These changes include adding complex carbohydrates such as raw uncooked cornstarch or switching to infant formulas with higher complex carbohydrate content. Small feeding volumes and restricting fluid intake also help minimize the intragastric pressure that promotes rapid emptying of stomach contents into the duodenum. There are some reports of continuous feeding regimens to avoid large fluxes in blood glucose levels, but this may decrease mobility and delay development of oral feeding skills in children. The use of α -glucosidase inhibitors such as acarbose has been studied in children with dumping syndrome. Acarbose interferes with the conversion of polysaccharides and reduces rapid carbohydrate absorption (Fig 5). Doses as low as 12.5 mg to start have been useful in helping achieve desired ranges of blood glucose without the adverse effects of flatulence, abdominal distention, and diarrhea. If children are administered acarbose for dumping syndrome, liver function tests should be closely monitored.

Lessons for the Clinician

- Dumping syndrome can result from Nissen fundoplication in pediatric patients.
- It is important to recognize the signs and symptoms of early and late dumping syndrome in a timely manner to ensure timely diagnosis and management.

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2 Jaw Pain, Pain on Deep Inspiration, and Severe Odynophagia in an 18-year-old Boy

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AUTHOR DISCLOSURE Drs Mangan, Shah, Troy, and Dawgert have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An 18-year-old boy presents with right-sided jaw pain, migratory body pains, decreased appetite, pain on deep inspiration, severe odynophagia, and dark urine. He had no history of sick contacts or international travel. He was evaluated a week earlier for a sore throat, moderate dysphagia, fever, and decreased energy. On physical examination at that time he was found to have an erythematous posterior pharynx, moderately enlarged tonsils, and cervical lymphadenopathy. His streptococcal antigen and Monospot test results were negative. He was prescribed corticosteroids and naproxen for pain and severe tonsillar enlargement.

Physical examination shows an erythematous posterior pharynx without exudates, severely enlarged tonsils, pleuritic chest pain on deep inspiration, and right mid-thoracic paraspinal tenderness. Vitals on presentation are a

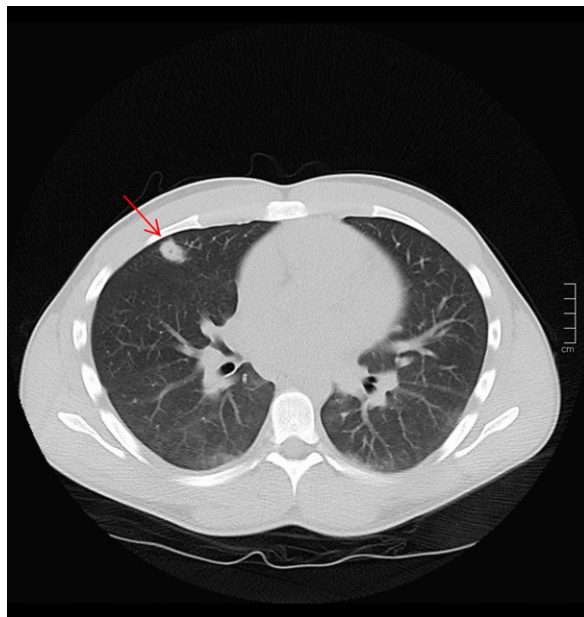


Figure 1. Axial computed tomographic scan of the thorax demonstrates an ovoid nodule (red arrow) in the right middle lobe with a small focus of central cavitation suspicious for a septic embolus.

temperature of 102.4°F (39.1°C) and a heart rate of 90 beats/min. The remaining physical examination results are normal.

He is hospitalized for further evaluation and treatment with ceftriaxone for concern for peritonsillar abscess.

Laboratory evaluation shows a white blood cell count of $24 \times 10^3/\mu\text{L}$ with 60% neutrophils and 25% bands, a platelet count of $115 \times 10^3/\mu\text{L}$ ($115 \times 10^9/\text{L}$), a blood urea nitrogen level of 30 mg/dL (10.7 mmol/L), and a creatinine concentration of 1.1 mg/dL (97.2 $\mu\text{mol/L}$). Urinalysis shows trace ketones, 5 to 9 red blood cells per high-power field, a urobilinogen level of 8 mg/dL, 2+ bilirubin, and 1+ protein.

A chest computed tomographic (CT) scan is performed because of pleuritic chest pain and shows interstitial pneumonia with possible septic emboli along with mediastinal and hilar lymphadenopathy (Fig 1). After 3 days, blood cultures are negative.

Given continued symptoms 3 days later, he is transferred to a tertiary care center, where additional imaging studies revealed the final diagnosis.

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/4/211>.

DISCUSSION

At the tertiary care center he developed acute respiratory distress, inability to turn or lift his head, and reduced leftward neck rotation and extension, with pain near the sternocleidomastoid in the region of the internal jugular vein. Pulmonary examination showed shallow tachypnea with decreased inspiratory effort and scant expiratory wheezes over the left lower lobe.

A CT of the neck with intravenous (IV) contrast showed a thrombosis of the middle segment of the right internal jugular and right parapharyngeal veins with surrounding edema and inflammation (Fig 2). With the jaw tenderness, internal jugular and parapharyngeal vein thrombophlebitis, and fever, the patient was diagnosed as having Lemierre syndrome and was transitioned to IV clindamycin from ceftriaxone. The patient's blood cultures grew *Fusobacterium necrophorum*. After 2 days he did not show much improvement so his antibiotics were changed to IV meropenem. He was discharged 2 days later in fair condition. The patient went home on IV meropenem 1 g every 8 hours for 6 weeks, enoxaparin 80 mg/0.8 mL subcutaneously every 12 hours, and *Lactobacillus rhamnosus* as a probiotic 2 times a day. The decision was made to send the patient home on enoxaparin to reduce his risk of further thrombosis and to allow for his current clot burden to dissipate.

THE CONDITION

Lemierre syndrome was first described in 1936 by French microbiologist Andre Lemierre, who came across 20 patients who had sepsis, metastatic pulmonary lesions, and *Bacillus funduliformis* (now known as *F necrophorum*). (1) This rare infectious syndrome is most commonly caused by *F necrophorum*, a gram-negative anaerobic bacillus that is part of the normal human oral flora. (1) The pathophysiology of this syndrome is unclear, and it is not known why *F necrophorum* becomes invasive. (2)

Lemierre syndrome was once a more common disease until the advent of antibiotics. Before the wide use of penicillin, Lemierre syndrome carried with it mortality of close to 90%. (1) Once the advent of penicillin occurred, this disease became virtually extinct. Between 1974 and 1995 there were only 100 published cases of Lemierre syndrome. (4) However, in the late 1990s the disease began a resurgence, and its incidence has near doubled and has continued to rise. There are 2 hypothesizes as to why Lemierre syndrome is reemerging, the first of which is that clinicians are trying to avoid unnecessary antibiotic drug use in pharyngitis that follows a typical viral pattern or in patients with a negative rapid streptococcal antigen

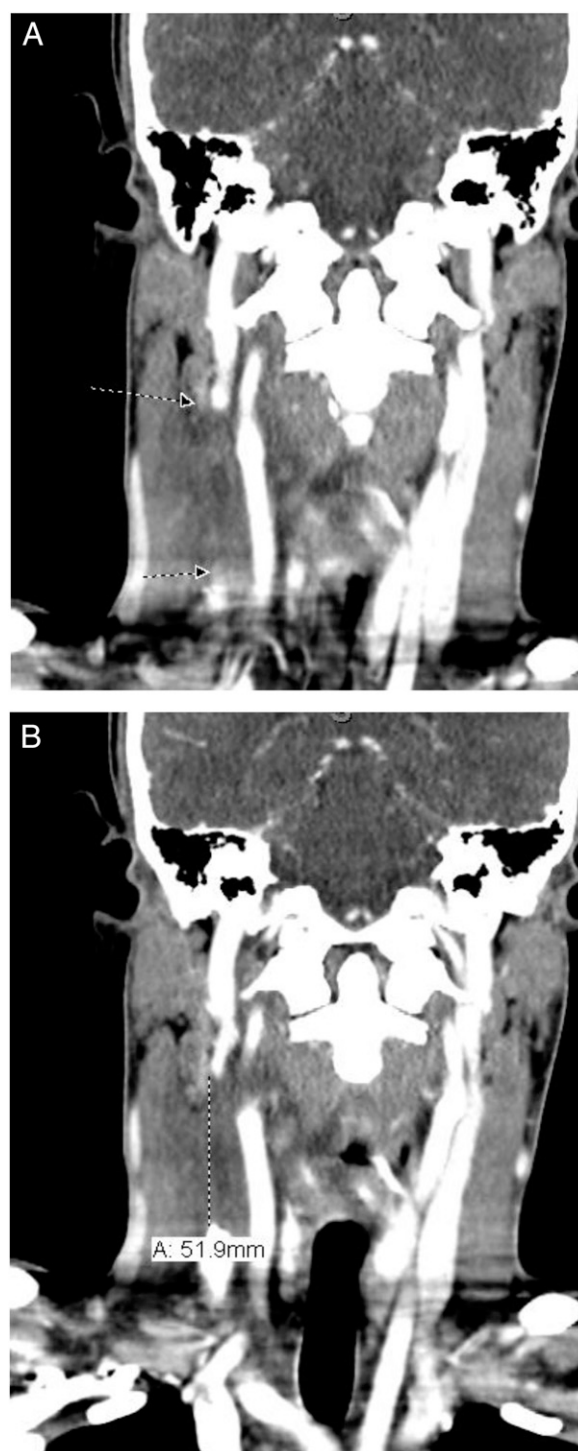


Figure 2. A. Reconstructed coronal computed tomographic scan of the neck with contrast demonstrates an intraluminal filling defect in the right internal jugular vein (arrows). B. The length of occlusion in the internal jugular vein was measured to be 51.9 mm. This filling defect is compatible with thrombus formation.

test result. (1)(3) The second hypothesis is simply that the reporting of Lemierre syndrome increased and that the incidence of the disease was at its current level. (1)

In 2010, it was estimated that pharyngitis caused by *F necrophorum* may be as common as that caused by group A streptococcus. (5) Furthermore, 1 in 400 cases of *F necrophorum* infection lead to complications, which include abscess, septicemia with pulmonary emboli, and Lemierre syndrome. (5) Case series have shown mortality associated with *F necrophorum* of 3% to 5% and morbidity of 10%. (5) Although the incidence of the disease has been increasing, it still remains a rare cause of pharyngitis. At this juncture it does not warrant treating all streptococcal antigen test–negative pharyngitis with antibiotic agents. This disease most commonly affects healthy adolescents and young adults, with a higher incidence in the winter and spring. (1) However, as demonstrated by the present case, the disease does not follow a strict seasonal pattern. The most common presenting symptom is pharyngitis, which usually precludes all other symptoms for 4 to 5 days. (1) On physical examination patients usually have a fever and may have a peritonsillar abscess. Symptoms typically progress over the next 5 to 12 days, with the development of neck pain, pleuritic chest pain, dyspnea, night sweats, and possible arthralgia. (1) Patients rapidly develop signs of endovascular septicemia, with tachycardia, fever, and leukocytosis. (2) The differential diagnosis includes infectious and malignant etiologies (Table 1). Lemierre syndrome is a clinical diagnosis based on the findings of gram-negative anaerobic bacteremia, metastatic septic pulmonary emboli, and thrombophlebitis of the internal jugular vein. Various imaging modalities are important to use to identify disease-defining pathology. Commonly, a chest CT scan is helpful in differentiating causes of pleuritic chest pain such as infection and malignancy. Ultrasonography of the neck can help identify any thrombosis in the jugular

venous system. Other diagnostic imaging can be helpful in identifying and treating other manifestations of this disease, such as meningitis and septic arthritis.

MANAGEMENT

Treatment of Lemierre syndrome requires 4 to 6 weeks of antibiotic drug therapy. (1) The antibiotic of choice is penicillin for Lemierre syndrome. (1)(5) It is important to note that *F necrophorum* is not sensitive to macrolides, which is the typical treatment for a penicillin-allergic patient with pharyngitis. (5) Therefore, if neck swelling occurs or there is progression of the symptoms the patient should be treated with clindamycin, metronidazole, imipenem, amoxicillin-clavulanate, or cefoxitin. (6) Surgical treatment for the removal of thrombosis is controversial, but abscesses may need to be drained. (1) Anticoagulation therapy is also controversial and not widely used. (1)

Lessons for the Clinician

- Pharyngitis caused by *Fusobacterium necrophorum* is thought to be as common as that caused by group A streptococci and carries with it a different set of complications, which can lead to significant mortality and morbidity. However, at this time, Lemierre syndrome remains rare and does not warrant prophylactic treatment.
- It is important to consider this diagnosis when pharyngitis does not follow the typical course seen with group A streptococcal infection.
- The typical patient with Lemierre syndrome is a young healthy adolescent or young adult with fever, pharyngitis, and a progressive clinical course that includes septicemia, metastatic septic pulmonary emboli, and thrombophlebitis of the internal jugular vein.
- The treatment for penicillin-allergic patients includes clindamycin and not macrolide if infection with *Fusobacterium* is suspected.

TABLE 1. Differential diagnosis based the presentation and progression of the signs and symptoms of Lemierre's Disease.

| DIFFERENTIAL DIAGNOSIS |
|--------------------------------|
| • Pyelonephritis |
| • Pharyngitis |
| • Viral URI |
| • Torticollis |
| • Uro-Sepsis |
| • Mononucleosis |
| • Pharyngeal/Tonsillar Abscess |
| • Lymphoma |
| • Tuberculosis |

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6 Liver Failure and Rash in a 6-week-old Girl

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AUTHOR DISCLOSURE Drs Mediratta, Schwenk, Rao, and Chitkara have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 6-week-old girl is admitted to the NICU with liver dysfunction and jaundice. One week before presentation she had developed an erythematous macular rash on the chest and extremities, oral thrush, and a low-grade fever. Physical examination reveals jaundice, hepatosplenomegaly, and a desquamating macular rash on the left lower extremity. Her vital signs are normal for age. She was born to a 34-year-old G7P2321 woman via normal spontaneous vaginal delivery at 37 weeks' gestation. Birthweight was 3,060 g (35th percentile). The infant's mother had routine prenatal care, and her course was complicated by intrahepatic cholestasis of pregnancy. Results of first-trimester maternal *Treponema pallidum* enzyme immunoassay were negative.

Laboratory evaluation reveals acute liver failure, coagulopathy, conjugated hyperbilirubinemia, lymphocyte-predominant leukocytosis, disseminated intravascular coagulation, anemia, and thrombocytopenia. Laboratory test results are notable for hemoglobin level, 7.2 g/dL (72 g/L); total leukocyte count, 25,000/ μ L (25.0×10^9 /L) with 68% lymphocytes and 18% neutrophils; platelet count, 20×10^3 / μ L (20×10^9 /L); aspartate aminotransferase, 1,164 U/L (19.4 μ kat/L); alanine aminotransferase, 536 U/L (8.9 μ kat/L); albumin, 1.8 g/dL (18 g/L); international normalized ratio, 1.8; and partial thromboplastin time, 34.9 seconds. Her C-reactive protein level was elevated at 19.1 mg/L (181.9 nmol/L).

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/6/315>.

DISCUSSION

The differential diagnosis includes sepsis due to bacteria such as *Escherichia coli*, *Enterococcus*, *Klebsiella*, methicillin-resistant *Staphylococcus aureus*, and *T pallidum*. Potential viral pathogens include enterovirus, echovirus, adenovirus, parvovirus, Epstein-Barr virus, cytomegalovirus, herpes simplex virus (HSV), human immunodeficiency virus (HIV), human herpesvirus 6, and other viral hepatitis. Noninfectious possibilities include α_1 -antitrypsin deficiency, hemophagocytic lymphohistiocytosis, and acetaminophen toxicity.

Treatment with vancomycin, cefotaxime, and acyclovir was initiated on hospital admission. Vitamin K, fresh frozen plasma, platelets, and packed red blood cells were administered. Acyclovir therapy was discontinued based on negative HSV polymerase chain reactions from mucosal, blood, and cerebrospinal fluid (CSF) samples. Results of CSF VDRL testing and plasma HIV RNA polymerase chain reaction were also negative. Three days later, liver dysfunction, anemia, and thrombocytopenia resolved. Antibiotic therapy was narrowed to ampicillin based on a blood culture with growth of *Enterococcus faecalis*. Syphilis was confirmed by serum *T pallidum* particle agglutination assay (TPPA) and rapid plasma reagin (RPR) titer (1:64). After the diagnosis of congenital syphilis, the infant received 10 days of intravenous aqueous penicillin G followed by 1 intramuscular dose of benzathine penicillin G. Both parents subsequently tested positive for syphilis (TPPA, RPR) and were treated. The infant was discharged after a normal ophthalmologic and audiology evaluation, with anticipation of periodic follow-up and serial nontreponemal antibody testing. The infant continues to be followed in the Pediatric Infectious Disease Clinic and had a greater than 4-fold reduction in RPR titer 3 months after hospital discharge (RPR titer of 1:8).

The Condition

This infant has congenital syphilis despite negative maternal first-trimester treponemal test results. Congenital syphilis is caused by transplacental transfer of *T pallidum*, a spirochete that is sensitive to penicillin. The incidence of congenital syphilis in the United States increased between 2012 and 2014. In 2014, there were 12 cases of congenital syphilis per 100,000 live births. (1) The incubation period of syphilis is typically 3 weeks but ranges from 10 to 90 days. (2) Risk factors for congenital syphilis include lack of prenatal care, substance abuse, sexual promiscuity, history of sexually transmitted infections, or contact with anyone with sexually transmitted infections. (3) Syphilis infection can occur throughout pregnancy and can result in miscarriage, stillbirth, prematurity, neonatal death, and congenital syphilis. (4)

The involvement of the placenta and subsequent hematogenous dissemination of *T pallidum* to the infant helps explain the multitude of clinical manifestations of congenital syphilis. Congenital syphilis is classified as early congenital syphilis, affecting infants from birth to 2 years old, and late congenital syphilis, affecting infants older than 2 years. Most infants with early congenital syphilis are asymptomatic at birth but can develop poor feeding, hepatomegaly, splenomegaly, jaundice, hemolytic anemia, diffuse intravascular coagulation, thrombocytopenia, pneumonitis, nephrotic syndrome, rhinitis, maculopapular rash, generalized lymphadenopathy, fever, central nervous system dysfunction, and osteochondritis during the first few weeks after birth. (5) Manifestations of late congenital syphilis include interstitial keratitis, saddle nose, saber shins, Hutchinson teeth, eighth nerve deafness, mental delay, and convulsive disorders. (5) Concurrent bacterial sepsis, secondary to bacterial translocation across the gastrointestinal mucosal barrier, has also been reported. (6)

Diagnosis

Because *T pallidum* cannot be readily cultured, syphilis is typically diagnosed using a screening nontreponemal test followed by a confirmatory treponemal test. Nontreponemal testing includes the VDRL and RPR tests. Treponemal tests include TPPA, *T pallidum* enzyme immunoassay, *T pallidum* chemiluminescent assay, and fluorescent treponemal antibody absorption. A reactive nontreponemal test result needs to be confirmed by treponemal testing because the sensitivity of RPR and VDRL tests to detect primary syphilis is 86% and 78%, respectively. (7) The RPR test works by detecting lipoidal material released by cells that are infected with *T pallidum*. The RPR test results can become positive from treponemal infections as well as nontreponemal conditions. False-positives for nontreponemal tests occur in 1% to 2% of the US population and can be due to other infections, including hepatitis, varicella, measles, HIV, and mononucleosis; pneumonia; autoimmune disease; injection drug use; lymphoma; tuberculosis; malaria; and pregnancy. (8)(9) Because nontreponemal test results parallel disease activity, they are also used to monitor response to therapy. In congenital syphilis, the RPR and VDRL tests should show at least a 4-fold reduction in titer by the third month after treatment. (7) Fluorescent treponemal antibody absorption is the most commonly used treponemal confirmatory test, and it has sensitivity of 84% and specificity of 97% to detect primary syphilis. (7) Unlike nontreponemal tests, the titers from treponemal tests do not correlate with disease activity and cannot be used to monitor response to therapy.

Treatment

The *Red Book* has recommendations, summarized herein, about the evaluation of infants who are born to mothers with a reactive serologic test for syphilis. (2) Mothers who have positive results of nontreponemal testing, such as RPR or VDRL, should receive a treponemal test. A negative treponemal test result strongly excludes the possibility of congenital syphilis. If a mother has a reactive treponemal test during the pregnancy, then evaluation of the infant is influenced by the mothers' treatment of syphilis.

If a mother who had syphilis was adequately treated with penicillin before the pregnancy, has either a low VDRL titer of 1:2 or less or a low RPR titer of 1:4 or less during the pregnancy, and the infant has normal examination findings, then the infant does not need an evaluation or treatment.

If the mother with syphilis was treated with penicillin more than 4 weeks before delivery and there is no evidence of maternal reinfection during the pregnancy based on maternal syphilis titers, then the infant should be tested for syphilis by RPR/VDRL testing. If the infant has abnormal physical examination findings and the infant's nontreponemal test is not 4-fold or greater than the mother's nontreponemal test, then the infant needs to be evaluated and treated for congenital syphilis. Infants who have 4-fold or greater nontreponemal titers also need to be evaluated and treated. Evaluation includes complete blood cell count, CSF examination for cell count, protein, glucose, and quantitative VDRL testing. Other tests should be ordered if clinically indicated, such as chest radiographs, long-bone radiographs, eye examination, liver function tests, neuroimaging, and auditory brainstem response.

Penicillin remains the drug of choice for the treatment of congenital syphilis. Treatment for congenital syphilis includes aqueous penicillin G 50,000 U/kg every 12 hours if 1 week of age or younger or every 8 hours if older than 1 week. Another option is procaine penicillin G 50,000 U/kg intramuscularly as a single daily dose for 10 days. If the infant's nontreponemal test is not 4-fold or greater than the mother's nontreponemal test, then the infant can be treated with one single dose of benzathine penicillin G 50,000 U/kg intramuscularly if the infant has normal physical examination findings. These infants' nontreponemal titers should be followed monthly until the results are negative.

If a mother is not treated with penicillin for syphilis during the pregnancy, if the treatment is not documented, if the treatment occurred 4 weeks or less before the delivery, if a nonpenicillin drug was used, or if there is a 4-fold or greater increase in maternal syphilis titers, then the infant

needs to be evaluated for congenital syphilis. If the infant's physical examination findings are normal, if the syphilis evaluation results are normal, and if the infant's nontreponemal titers are the same or less than 4-fold the maternal nontreponemal titers, then the infant should be treated with 10 days of penicillin G, either intravenously or intramuscularly, or with a single dose of benzathine penicillin G 50,000 U/kg intramuscularly. Most experts recommend 10 days of treatment. If the infant's physical examination findings are abnormal, if the evaluation results are abnormal, or if the infant's nontreponemal titer is at least 4-fold greater than the maternal nontreponemal titer, then the infant should be treated with 10 days of either aqueous or procaine penicillin. All infants with congenital syphilis should also be tested for other coinfections, including HIV, hepatitis B, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis*.

Infants with skin or mucus membrane lesions should be cared for with gloves until 24 hours of therapy has been completed because nasal secretions, blood, and discharge from lesions are potentially infectious. (6) A mother with syphilis may continue to breastfeed her infant as long as she does not have active lesions on her breast. There is no evidence that syphilis is transmitted through human milk among mothers without active breast lesions. (10) Laboratory follow-up after treatment includes VDRL/RPR testing every 3 months until the titer is negative or has decreased at least 4-fold.

Lessons for the Clinician

- A negative maternal first-trimester test for syphilis during pregnancy does not negate the risk of infants developing congenital syphilis.
- The Centers for Disease Control and Prevention (CDC) recommends that all pregnant women be tested for syphilis during the first trimester of pregnancy. Women at high risk for syphilis, including those who live in areas of high syphilis morbidity, who are previously untested, or who had a positive screening test result, should be screened for syphilis during the third trimester and at delivery. (11)
- The rise of congenital syphilis presents an opportunity for pediatricians and neonatologists to partner with obstetricians, family practitioners, internists, and public health departments about how to best screen for and prevent congenital syphilis.
- As long as syphilis continues to spread among adults, congenital syphilis will continue to pose a serious threat for infants.

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1 Microcephaly, Skeletal Dysplasia, and Immunodeficiency in a Newborn

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EDITOR'S NOTE

The editors of *Pediatrics in Review* greatly appreciate feedback from readers, many of whom made it clear that reading the case reports in print form is still preferred. So, in response to your input, this issue takes us "back to the future" with all *Index of Suspicion* cases again appearing in the print journal as well as online. Thanks for reading, and thanks for the feedback!

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

A newborn is admitted to the NICU for evaluation given abnormal prenatal ultrasonography findings of small for gestational age and shortened long bones. He was born at 39⁺¹ weeks' gestation to a nonconsanguineous, healthy, 32-year-old gravida 2, para 1 mother and a healthy 33-year-old father by elective cesarean delivery. The pregnancy and labor were normal. No invasive testing was performed prenatally. Apgar scores were 9 and 9 at 1 and 5 minutes, respectively.

We invite readers to contribute *Index of Suspicion* cases through the PIR manuscript submission system at: <https://mc.manuscriptcentral.com/pir>.

AUTHOR DISCLOSURE Dr Belal and Ms Malcolmson have disclosed no financial relationships relevant to this article. Dr Day-Salvatore has disclosed that she receives research grant funding for longitudinal studies from Sanofi Genzyme and grant funding from the New Jersey Department of Health Special Child Health and Early Intervention Services. She also serves as a lysosomal storage disease expert for Sanofi Genzyme and receives travel reimbursement and honoraria from the company. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Radiograph of the patient's right arm showing relative shortening of the humerus.



Figure 2. Radiograph of the patient's left forearm. Note the distal metaphyseal cupping of the radius and ulna.

The maternal family history is remarkable for endometrial cancer in the grandmother and mesothelioma and prostate cancer in the great-grandfather. A paternal great-aunt had breast cancer and the paternal great-grandmother had ovarian cancer. The couple has a healthy 3-year-old daughter. Physical examination is notable for head circumference of 31.5 cm (<3rd percentile), weight of 2,955 g (16th percentile), length of 47.5 cm (18th percentile), mild shortening of proximal long bones more notable in upper than lower extremities, and shortening of digits. Physical examination findings are otherwise normal. Skeletal survey radiographs show rhizomelic shortening of long bones (Fig 1), metaphyseal cupping of the proximal humeri, distal femora, radii, ulni (Fig 2), tibiae and fibulae, trident acetabula (Fig 3), and hypoplastic metacarpals (Fig 4). The state newborn screen returns positive for severe combined immunodeficiency (SCID) later classified as leaky SCID with further lymphocyte studies. A spondyloepimetaphyseal dysplasia gene sequencing panel shows a pathogenic mutation in the *FGFR3* gene, which is associated with achondroplasia. However, because the findings of microcephaly and SCID are not consistent with achondroplasia, and neither are the radiographs and physical examination findings pathognomonic, whole exome sequencing is performed, which reveals the diagnosis.

DISCUSSION

Whole exome sequencing confirmed a *de novo* pathogenic mutation in the *FGFR3* gene, which is associated with achondroplasia and homozygous variants in the *NBN* gene, which is associated with Nijmegen breakage syndrome (NBS).

Achondroplasia is an autosomal dominant skeletal dysplasia caused by mutations in the fibroblast growth factor receptor 3 gene (*FGFR3*). It is characterized by macrocephaly, short stature, shortening of arms and legs, brachydactyly, kyphoscoliosis, and lumbar lordosis.

Nijmegen breakage syndrome is a rare autosomal recessive chromosomal instability syndrome caused by pathogenic variants in the *NBN* gene located at chromosome 8q21.3. It is characterized by microcephaly, growth restriction, immunodeficiency, radiation sensitivity, and predisposition to malignancy.

MASKING OF BOTH CONDITIONS

The newborn did not exhibit the classic clinical signs of achondroplasia such as macrocephaly, depressed nasal bridge, frontal bossing, and narrow chest; however, he presented with moderate microcephaly (head circumference of 31.5 cm), which is also not typical of patients with NBS who classically have severe microcephaly at birth. This is an example of how the presence of 2 genetic conditions can mask the classic clinical findings of each other.

PATHOPHYSIOLOGY

The protein product of the *NBN* gene is nibrin, which plays a key role in regulating the activity of protein complexes that are involved in end-processing of normal and mutated DNA double-strand breaks generated by ionizing radiation. If DNA double-strand breaks are not repaired, they result in genomic instability, gene mutations, or chromosome rearrangements that can lead to cancer. (1) Nibrin also plays a role in lymphocyte maturation and immunoglobulin class switching. (2)

EPIDEMIOLOGY

Although NBS is a rare disease, its incidence rates are increasing given advances in technology and increased awareness of the condition. The highest prevalence is in patients with eastern European ancestry, particularly from Poland, Slovakia, and Czech Republic. (3) Our patient's father is of Slovakian and mixed European descent, and his mother is of mixed European ancestry.

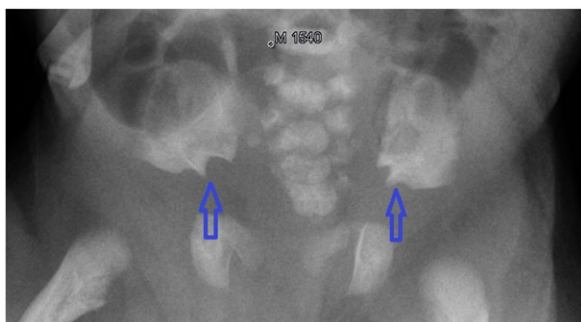


Figure 3. Radiograph of the patient's pelvis. Arrows pointing at the trident acetabula.

THE HOMOZYGOUS PATIENT

Nijmegen breakage syndrome is an autosomal recessive disease, hence it necessitates the inheritance of 2 copies of pathogenic variants in the *NBN* gene to manifest.

The main clinical finding in infants with NBS is severe progressive microcephaly that is present at birth. Head circumference is usually 10 to 12 cm less than the mean. (4) It is associated with mild-to-moderate intellectual disability and decline in cognitive skills; however, gross motor development is typically not affected. Patients may be appropriate or small for gestational age at birth, then they develop growth restriction over the first 2 years after birth, followed by normal growth velocity. Given the period of initial growth delay, adult height is typically within the lower normal range. Children with NBS have characteristic facial features, including upslanting palpebral fissures, sloping forehead, prominent midface, long nose, and receding mandible. Some patients with NBS also develop cutaneous findings, such as café-au-lait macules, hypopigmented skin lesions, and cutaneous noncaseating granulomas. (5)(6)

Cancer is the most common cause of death in patients with NBS, with lymphoma and leukemia accounting for most. The increased risk of cancer is due to chromosomal instability and sensitivity to ionizing radiation. (7)

Patients with NBS have a reduced number of B and T lymphocytes, resulting in defective humoral and cellular immunity, with sinopulmonary infections being the most common, which can result in bronchiectasis and chronic lung disease. Patients may have low T-cell receptor excision circles (TRECs) due to low T-lymphocyte count at birth; therefore, in states where a TREC assay is performed as part of newborn screening, a positive screen for SCID may be the first presentation of NBS. (8)

THE HETEROZYGOUS PATIENT

Heterozygous carriers of pathogenic variants in the *NBN* gene are typically asymptomatic; however, they have an

increased risk of developing cancer over their lifetime, particularly breast and prostate cancer. (9) Our patient has a significant family history of cancer, which may be attributed to the pathogenic variants in *NBN* gene. The patient's sister, mother, father, maternal grandmother, and 2 great-aunts tested positive for the familial pathogenic variant in *NBN*.

TREATMENT AND PROGNOSIS

There is no specific treatment for NBS. Intravenous immunoglobulin is given if immunoglobulin levels are low, and antibiotic prophylaxis should be instituted. Live vaccines must be avoided.

Our patient's mother was advised to avoid breastfeeding due to a risk of cytomegalovirus transmission (which can be potentially life-threatening in immunocompromised patients) and to use trimethoprim-sulfamethoxazole and fluconazole for prophylaxis of *Pneumocystis jiroveci* pneumonia and disseminated candidiasis, respectively. Intravenous immunoglobulin treatments were also administered within the first month after birth due to the defective humoral immune system.

Household members of patients with combined humoral and cell-mediated immunodeficiencies such as



Figure 4. Radiograph of the patient's right wrist. Note the relatively short length of the metacarpal bones.

NBS are encouraged to receive all vaccinations, including live vaccines, according to schedule except for the oral polio vaccine (which is no longer available in the United States at the time of this writing; however, it is still available in many countries worldwide) due to the potential risk of shedding the virus in the stool and infecting the immunocompromised individual. (10) The Infectious Diseases Society of America also advises against administering the live attenuated influenza vaccine to household contacts of a patient with SCID and individuals who live with an immunocompromised hematopoietic stem cell transplant recipient within 2 months after the transplant. (10)

Parents and primary care providers of patients with NBS should be aware of the increased cancer risk. Prompt investigation should be initiated if patients develop symptoms. All forms of ionizing radiation, such as radiographs or computed tomographic scans, must be avoided unless absolutely necessary.

Patients with NBS are very sensitive to radiation treatment and chemotherapy; therefore, if they develop malignancy, the radiation dosage should be limited. (11) Hematopoietic stem cell transplant has been successfully used in some patients who developed severe immunodeficiency or

cancer. Our patient's older sister is a human leukocyte antigen (HLA)-compatible donor; however, the risks associated with hematopoietic stem cell transplant outweigh the benefits at this time. (12)

Patients with NBS have a reduced life expectancy due to the early onset of malignancies. The International Nijmegen Breakage Syndrome Study Group estimates the age at death to range from 2 to 21 years. (7)

Lessons for the Clinician

- Physicians should be aware that an individual may have more than 1 genetic condition and that the clinical manifestation of 1 condition can mask or alter the presentation of the other.
- Clinicians should be aware of the clinical features of Nijmegen breakage syndrome (NBS) and realize that an abnormal newborn screen for severe combined immunodeficiency along with microcephaly can be the initial presenting features of NBS.
- Clinicians should understand that NBS is associated with cancer risks in both homozygotes and heterozygotes.

References and for this article are at <http://pedsinreview.aappublications.org/content/39/7/359>.

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4 Muscle Rigidity in a 5-year-old Boy

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AUTHOR DISCLOSURE Drs Ference, Paprocki, Boyd, Butler, and Bratcher have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy, unimmunized 5-year-old boy is found to have apnea, muscle rigidity, and trismus when paramedics arrive at his home. He has severe arching of his back, with only his head and buttocks touching the gurney. Symptoms began with an intermittent dry cough and worsening dysphagia 2 days ago. He has no history of fevers, vomiting, diarrhea, or headache. His family denies any recent medication exposures, wounds, or direct contact with animals or insects. He is intubated for respiratory failure but continues to have episodes of jaw clenching associated with bradycardia and desaturations. He is admitted to the PICU for further evaluation and management.

On admission, he continues to have episodes of muscle spasm and spinal rigidity despite increasing dosing of continuous dexmedetomidine, fentanyl, and midazolam. The initial examination reveals a normal electrolyte panel, blood calcium level, C-reactive protein level, complete blood cell count, and head computed tomographic scan. His cerebrospinal fluid shows a white blood cell count of $2/\mu\text{L}$ ($<0.01 \times 10^9/\text{L}$), a glucose level of 96 mg/dL (5.3 mmol/L), and a protein level of 0.021 g/dL (0.21 g/L). He is started on empirical antibiotic treatment with vancomycin, ceftriaxone, and metronidazole. Results of further testing, including cerebrospinal fluid enterovirus, varicella, and herpes simplex virus polymerase chain reactions; a comprehensive drug screen; magnetic resonance imaging of the head/neck/spine; and strychnine testing, return negative. Continuous video electroencephalography (EEG) to rule out underlying seizure activity supported the eventual diagnosis.

The Case Discussion and Suggested Readings appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/5/262>.

DISCUSSION

During hospital admission, the patient continued to have severe muscle spasms and trismus to the point of dislodging 2 upper incisors after clamping down on his endotracheal tube. Along with his rigidity, he was noted to have autonomic instability with bradycardia, tachycardia, hypertension, and desaturations. He had several episodes of severe chest wall rigidity and laryngospasm, inhibiting effective bag-mask ventilation despite intubation. Continuous video EEG revealed continuous muscle contraction concerning for dystonia versus tetany. Based on his clinical status and EEG findings, he was diagnosed as having tetanus due to an unknown source.

The Condition

Tetanus is an acute paralytic illness caused by *Clostridium tetani*, a gram-positive, anaerobic, spore-forming bacillus found in soil and animal intestinal tracts. Infection is rare in the United States, with fewer than 40 confirmed cases reported to the Centers for Disease Control and Prevention (CDC) each year. Most cases occur in the setting of no vaccination, inadequate vaccination, or inadequate wound care. An obvious contaminated wound is seen in most cases, but in approximately 5% no wound is noted. The case-fatality rate in the United States from 2001 through 2008 was 13.2%.

Clostridium tetani produces the exotoxin tetanospasmin, which acts in the central nervous system by irreversibly blocking inhibitory glycine and γ -aminobutyric acid-releasing neurons. This results in the clinical manifestations of tetanus, including trismus (lockjaw), risus sardonicus (sardonic smile with facial and buccal spasm), and opisthotonos (extreme body hyperextension). Other symptoms include dysphagia, irritability, and pharyngeal/laryngeal spasm. The clinical triad of rigidity, muscle spasms, and autonomic dysfunction can lead to severe pain, fractures, respiratory failure, and acute cardiac death. Diagnosis is generally made based on clinical findings. Often, *C tetani* is difficult to isolate in culture; therefore, negative culture results do not rule out the diagnosis. Although EEG was used in the present patient, this is not necessary for diagnosis. Other diagnoses to consider include rabies, trismus from dental or retropharyngeal abscess, hypocalcemia, dystonic drug reaction, seizure, and strychnine poisoning.

Management

The mainstay of treatment is supportive care with emphasis on maintaining airway patency. Sedation and neuromuscular blockade are commonly required to manage rigidity

and spasms. Metronidazole and tetanus immune globulin (TIG) are recommended as primary tetanus therapy. When autonomic dysfunction is present, treatment with magnesium sulfate and/or β -blockade may be beneficial. Additional supportive measures include close monitoring of the patient's hemodynamics, providing nutrition (high metabolic demand from increased muscular activity), and limiting environmental stimuli. Recovery depends on regeneration of new neuron synapses to restore muscle relaxation.

Prevention

Prevention strategies of tetanus can be divided into 3 categories: primary, secondary, and tertiary. Primary prevention is given with tetanus vaccine: 3 doses in the first year, a fourth dose at 15 to 18 months, and a fifth dose between 4 and 6 years. A booster vaccine should then be given every 10 years. Secondary prevention includes use of TIG and a tetanus vaccine for wounds that are at risk for contraction of tetanus. Patients at risk include those who are not fully immunized or who have a severe cut, dirty wound, or burn. Tertiary prevention is achieved with a tetanus vaccine at the time of infection, as having tetanus does not confer immunity. Vaccine adverse effects include pain, redness, or swelling at the injection site, and rarely an Arthus reaction. Contraindications include anaphylaxis to a previous dose of this vaccine, severe allergy to a vaccine component, coma, or repeated seizures within 7 days of receiving the vaccine.

Clinical Course

The patient ultimately required neuromuscular blockade with continuous vecuronium infusion, treatment with baclofen and dantrolene, and tracheostomy placement. He was treated with human TIG and 14 days of metronidazole. He was slowly weaned off all of his medications, decannulated, and discharged on hospital day 26. Before discharge, he received his first tetanus vaccination.

Lessons for the Clinician

- Tetanus is a rare but potentially deadly condition related to the exotoxin tetanospasmin produced by *Clostridium tetani*.
- Clinical symptoms include trismus (lockjaw), risus sardonicus (sardonic smile with facial and buccal spasm), opisthotonos (extreme body hyperextension), dysphagia, irritability, and pharyngeal/laryngeal spasm.
- The clinical triad of rigidity, muscle spasms, and autonomic dysfunction can lead to severe pain, fractures, respiratory failure, and acute cardiac death.

- The diagnosis of tetanus is made based on clinical findings and a history suggestive of possible tetanus exposure and/or inadequate immunization.
- Treatment includes metronidazole, tetanus immune globulin, and supportive care measures to ensure airway patency and treat muscle rigidity and spasm.

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3 Ophthalmoplegia and Unsteady Gait in an 11-year-old Boy

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AUTHOR DISCLOSURE Drs Bassal and Lupo have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy 11-year-old boy is admitted to the hospital for 2 days of new-onset blurry vision, diplopia, and unsteady gait. He denies recent trauma, dizziness, weakness, headaches, nausea, vomiting, diarrhea, fever, and travel. The patient denies recent ingestion of alcohol, illicit drugs, medications, or toxins. Further questioning reveals a 1-day history of coughing, sneezing, and watery eye discharge occurring 1 week earlier that seemingly improved after antihistamine use.

On admission, his vital signs are as follows: temperature, 98.5°F (36.9°C); pulse, 83 beats/min; respiratory rate, 18 breaths/min; blood pressure, 129/86 mm Hg; and oxygen saturation, 100% in room air. Physical examination reveals a well-nourished boy with appropriate affect and mentation. Ophthalmologic examination is significant for left esotropia and mild bilateral hypertropia. Extraocular movements are painless, with incomplete abduction of both eyes, worse on the left. Consensual pupillary response is absent, and the pupils are dilated to 7 mm at baseline, with a sluggish direct response to light. There is no optic nerve edema. Neurologic examination is otherwise significant for dysmetria, which improves somewhat with covering 1 eye, and a tentative gait with unsteadiness concerning for gait ataxia. Reflexes are difficult to elicit but present, and there is no muscle weakness.

Urine toxicology screen is negative. Head computed tomography and brain magnetic resonance imaging findings are normal. Lumbar puncture reveals an opening pressure of 17 cm H₂O. Cerebrospinal fluid (CSF) analysis reveals no white blood cells, a protein level of 0.028 g/dL (0.28 g/L), and a glucose level of 65 mg/dL (3.6 mmol/L). Results of CSF and serum viral studies are negative.

The patient's vital signs and condition remain stable, but reflexes are absent on examination the following day. Treatment is initiated based on clinical findings, and a serum antibody test confirms the clinical suspicion.

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/1/39>.

DISCUSSION

Differential Diagnosis

The initial differential diagnosis for this patient with cranial nerve VI and cranial nerve III dysfunction and gait problems (likely ataxia) with preserved strength and cognition included intracranial tumor, central nervous system infection, demyelinating disease, Guillain-Barré syndrome (GBS), intoxication, and acute cerebellar ataxia.

Because neuroimaging results were normal, we were able to rule out tumor and some forms of demyelinating disease, such as acute demyelinating encephalomyelitis and multiple sclerosis. Urine drug screen acetaminophen and salicylate levels were negative, making toxic ingestion unlikely. Our patient did not have a fever or signs of infection, and human immunodeficiency virus (HIV) serology was negative. Results of serum and CSF herpes simplex virus, varicella-zoster virus, and enterovirus studies were also negative.

When his cranial nerve abnormalities persisted and he began to have more definitive ataxia on examination and absent tendon reflexes, the diagnosis of GBS, especially the Miller Fisher syndrome (MFS) variant, became much more likely. Although albuminocytologic dissociation is expected on CSF studies, this abnormality is often not present early in the course of the disease.

With GBS in mind, we sent a serum ganglioside antibody panel, which returned significant for elevation of antiganglioside anti-GQ1b immunoglobulin G antibody, confirming our diagnosis of the MFS variant of GBS.

The Condition

The MFS is rare, with an incidence of 1 in 1 million and accounting for 5% of patients with GBS. (1) Clinically, it consists of the classic triad of areflexia, ataxia, and ophthalmoplegia. (2) Our patient displayed this triad during his hospital admission, although the areflexia developed later in the course. His oculomotor paresis came in the form of cranial nerve VI palsy demonstrated by left esotropia with incomplete eye abduction, in addition to cranial nerve III palsy evidenced by hypertropia and the pupillary findings, which are likely secondary to the nerve's efferent limb for consensual light reflex. The ophthalmoplegia characteristic of MFS is particularly associated with an elevation of antiganglioside anti-GQ1b immunoglobulin G antibody, which is elevated in more than 90% of patients. (3)

Because MFS is a rare variant of GBS, it results from peripheral nerve demyelination after an initial insult is thought to spur an autoimmune response. (1) The most common inciting cause is an infectious process, with *Campylobacter jejuni* being the most commonly implicated. This

is thought to occur through molecular mimicry, as studies have demonstrated that lipopolysaccharide epitopes from *C. jejuni* may mimic human gangliosides, leading to cross reactivity in affected patients. (4) GQ1b is one such anti-ganglioside antibody and is notably concentrated in the cranial nerves, particularly III and VI, as demonstrated by cranial nerve enhancement on neuroimaging studies. (5)

There are numerous other infectious etiologies for MFS reported, including HIV, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, *Escherichia coli*, influenza A, and mumps. Additional causes include various cancers, autoimmune conditions, and tumor necrosis factor inhibitor medication. (6) Our patient's case is unique in that the most probable inciting cause was an episode that resembled allergic rhinitis based on the symptom description and improvement after diphenhydramine and cetirizine therapy. To the author's knowledge, this is the only such case of MFS in the literature caused by allergic rhinitis.

Management and Outcomes

The standard treatment for MFS is intravenous immunoglobulin (IVIg) or plasmapheresis, as it is in GBS. A retrospective study by Mori and colleagues demonstrated that IVIg therapy slightly sped up the recovery of ophthalmoplegia and ataxia in patients with MFS. (7) However, IVIg therapy and plasmapheresis are not warranted for all affected individuals. In fact, mildly affected patients may be closely observed because most patients have good outcomes, with recovery at 10 weeks on average. (8) Although MFS rarely includes dysautonomia or progresses to respiratory failure, as is more commonly seen with standard GBS, approximately one-third of patients have residual symptoms, and there are rare cases of recurrence, with a notable case report describing 2 children with recurrent MFS. (9)

Our patient was treated with IVIg 400 mg/kg per dose for 5 doses. By the time of hospital discharge, he remained areflexic, with improvement of his gait and double vision. On neurology clinic follow-up 2 weeks after discharge, he was noted to have a normal pupillary response to light but still had lateral gaze palsy. Intermittent eye patching provides comfort, and he is back in school, although he needs extra time to get to and from classes. As of the time of this report, he continues to follow up with outpatient neurology and neuro-ophthalmology.

Lessons for the Clinician

- Miller Fisher syndrome (MFS) is a rare variant of Guillain-Barré syndrome that presents with the triad of areflexia, ataxia, and ophthalmoplegia.
- Although *Campylobacter jejuni* is often implicated, there are various other inciting factors leading to the autoimmune response causing the disease.

- When suspected, serum antiganglioside studies should be analyzed because elevation of antiganglioside anti-GQ1b immunoglobulin G antibody is highly specific for MFS.
- Intravenous immunoglobulin therapy has been shown to slightly accelerate recovery in MFS and should be used in severe cases.

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Case 3: Ophthalmoplegia and Unsteady Gait in an 11-year-old Boy

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Pediatrics in Review

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Case 3: Ophthalmoplegia and Unsteady Gait in an 11-year-old Boy

Frederick Bassal and Pamela Lupo

Pediatrics in Review 2018;39;39

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The online version of this article, along with updated information and services, is located on the World Wide Web at:

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4 Persistent Lung Lesion in a 6-year old Boy with Sickle Cell Disease

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AUTHOR DISCLOSURE Drs Zaidi and Henry have disclosed no financial relationships relevant to this article. Dr Callaghan has disclosed that he is involved in a Pfizer-funded investigator-initiated research study of sickle cell disease; that he is site principal investigator for 4 studies by Genentech and for studies by Sancillo and Global Blood Therapeutics; that he receives honoraria from Bayer, Shire, Novo Nordisk, and Genentech for speaking engagements; that he has participated in advisory boards for Shire, Genentech, Pfizer, Bayer, and Grifols; and that he owns stock in Alnylam. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 6-year-old boy with sickle cell disease (hemoglobin SS), who is on a long-term exchange transfusion program for repeated splenic sequestration and abnormal transcranial Doppler findings, presents to the emergency department with upper respiratory symptoms and a sore throat. On physical examination he appears well. His temperature is 99.3°F (37.4°C), heart rate is 100 beats/min, respiratory rate is 18 breaths/min, blood pressure is 110/65 mm Hg, and oxygen saturation is 100% on room air. A chest radiograph shows a lesion in the left upper lobe (Fig 1), thought to be round pneumonia, and the child is started on cefepime and azithromycin. It is noted that a very similar lesion was seen on radiography at the time of a previous hospital admission for upper respiratory infection 6 months earlier. Due to persistence of the opacity, a chest computed tomographic scan is performed and reveals a well-circumscribed round mass measuring 4 × 4 × 4 cm in the left hilum, centered at the bifurcation of the upper and lower bronchi (Fig 2). The mass is solid, homogeneous, and without calcification. A left thoracotomy and complete excision of the mass is completed. The specimen is sent to the pathology laboratory, and this leads to the eventual diagnosis.

DISCUSSION

Differential Diagnosis

Based on the history, physical examination, and radiographic findings, it is ascertained that this child has a round chest mass. This child was initially admitted to the hospital with bacterial pneumonia with focal consolidation. Pulmonary consolidations in children tend to be spherical, and the etiology of these "round pneumonias" is often *Streptococcus pneumoniae*. This would be the most common scenario in a healthy 6-year-old boy. However, these consolidations usually resolve rapidly after initiation of antibiotics and should not persist over several months.

In a child with sickle cell disease, one must account for the possibility of lesions of extramedullary hematopoiesis. Extramedullary hematopoiesis is the growth of hematopoietic cells in areas other than the bone marrow, and it can occur in settings of bone marrow replacement or hemolytic anemias. Although most frequently found in the liver, spleen, and lymph nodes, it can be found in the thymus, kidney, and retroperitoneum. Thoracic extramedullary hematopoiesis is infrequent but has been described in sickle cell disease. (1)

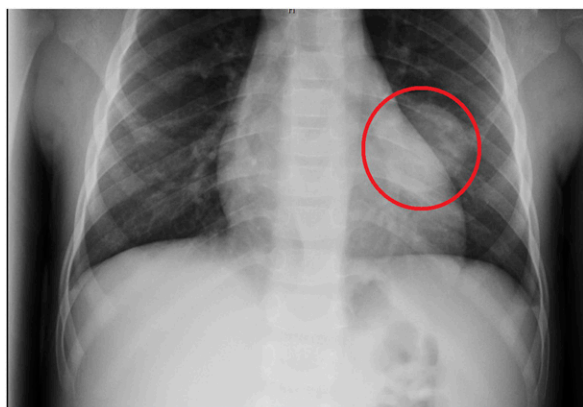


Figure 1. Chest radiograph depicting the presence of a focal rounded opacity overlying the left mid-lung measuring approximately 4.5 cm (red circle).

Finally, the exclusion of a neoplasm is mandated on the care team. This is generally achieved via biopsy and pathologic diagnosis. Our patient was found to have Hodgkin lymphoma on biopsy.

The Condition and Diagnosis

Hodgkin lymphoma accounts for approximately 7% of childhood cancers and 1% of childhood cancer deaths in the United States. (2) The evaluation of Hodgkin lymphoma begins with a thorough medical history, including assessing for the presence of "B" symptoms, including fever, weight loss, and drenching night sweats. Although not the case in our patient, a good history is vital in identifying the presence of potentially life-threatening complications, such as superior mediastinal or superior vena cava syndrome (orthopnea, swelling of the face or limb, etc), in patients with lymphoma. The most frequently found physical finding in these patients is lymphadenopathy. A laboratory profile can reveal abnormalities in the complete blood cell count, including neutrophilic leukocytosis, lymphopenia/lymphocytosis, eosinophilia, monocytosis, and anemia. The biochemical profile can reveal an elevated lactate dehydrogenase level, a low albumin level, and elevated markers of inflammation, including erythrocyte sedimentation rate, C-reactive protein, copper, and ferritin. It is important to remain cognizant of the possibility of lymphoma, even in the absence of any laboratory abnormalities, particularly in children who may have low-stage disease.

Imaging with computed tomography of the neck, chest, or abdomen may reveal lymph node or organ involvement. The metabolic activity of lymph nodes and extralymphatic organs can be evaluated by 18-fluoro-deoxyglucose positron emission tomography. Definitively, a lymph node or bone marrow biopsy is necessary to provide histologic confirmation of Hodgkin lymphoma.

The staging of Hodgkin lymphoma is based on the presence of involved lymph nodes or organs on one or both sides of the diaphragm. The presence or lack of B symptoms, extranodal disease, and bulky disease can also affect staging.

Although the histologic classification of Hodgkin lymphoma is beyond the scope of this article, broadly, the World Health Organization classifies 2 major subtypes of Hodgkin lymphoma: classical and nodular lymphocyte predominant. Classical Hodgkin lymphoma includes nodular sclerosis, mixed-cellularity, lymphocyte-rich, and lymphocyte-depleted subtypes. Children with nodular lymphocyte-predominant or mixed-cellularity subtypes are more likely to have early-stage disease and to lack systemic symptoms.

Management

Contemporary combined-modality therapy has resulted in excellent event-free survival rates in children with Hodgkin lymphoma. The regimen of ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide) serves as the backbone in current Children's Oncology Group Hodgkin lymphoma protocols. Radiotherapy is used as an adjunct for a subgroup of children with residual metabolically active disease or bulk mediastinal disease.

Individualized response-based therapy has allowed for both continued excellent survival rates as well as reduction of therapy-related toxicity, particularly long-term. This approach assesses disease response to chemotherapy to determine the need for intensification of treatment. Future efforts will focus on integration of new agents for further

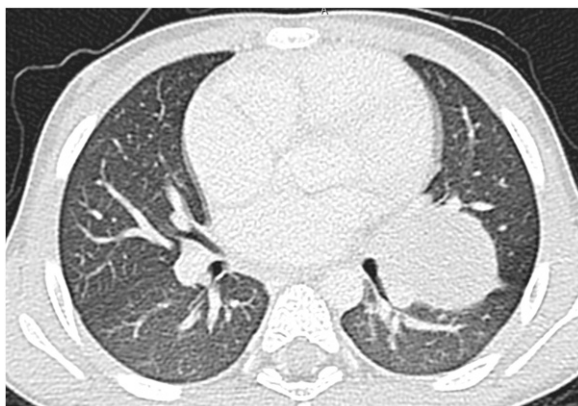


Figure 2. Computed tomographic scan of the chest showing a sharply margined, well-circumscribed round mass measuring approximately 3.7 × 3.8 × 3.3 cm in the anteroposterior, transverse, and cranial caudal dimensions, respectively, seen in the left hilum, centered at the bifurcation of the upper and lower bronchi. The mass appears solid and homogeneous in attenuation, without evidence of enhancement, necrosis, or internal calcifications.

reduction of late effects, as well as identification of biomarkers for risk stratification.

Lessons for the Clinician

- Acute chest syndrome and pneumonia are common diagnoses in sickle cell disease, but other etiologies must always be considered when caring for this group of children.

- Hodgkin lymphoma is a common pediatric cancer that can be effectively treated with combined-modality treatment regimens that include chemotherapy and radiotherapy.

References for this article are at <http://pedsinreview.aappublications.org/content/39/9/473>.



Index of Suspicion

3 Persistent Pharyngitis in a 14-year-old Girl

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AUTHOR DISCLOSURE Drs O'Halloran and Winn have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 14-year-old girl is admitted to the hospital with a 3-week history of sore throat leading to significantly decreased oral intake. She reports progressive worsening of a painful sore throat resulting in avoidance of nearly all oral intake and an associated 22-lb weight loss. She has presented to care twice, 2 weeks and 2 days earlier. During each of those visits, rapid group A streptococcal (GAS) antigen testing and follow-up GAS culture were negative. She was discharged with symptomatic care for presumed viral pharyngitis. She vomited twice but has not had fevers, cough, rash, or diarrhea. Her medical history is noncontributory. Her immunizations are up to date. She reports one lifetime sexual partner and reports condom use with every encounter.

On examination the patient is tachycardic to 150 beats/min, afebrile, and other vital signs are normal. Her mucous membranes are dry. She has posterior and anterior cervical lymphadenopathy, palatal petechiae, and erythematous enlarged tonsils with mild exudates. Results of cardiac, pulmonary, abdominal, and complete neurologic examinations are normal.

Initial laboratory tests are notable for an elevated white blood cell count of 20,500/ μ L (20.5×10^9 /L), a sodium level of 154 mEq/L (154 mmol/L), a blood urea nitrogen level of 32 mg/dL (11.4 mmol/L), and a creatinine level of 1.03 mg/dL (91 μ mol/L) (her baseline creatinine level is 0.4 mg/dL [35 μ mol/L]). Further laboratory testing reveals the diagnosis.

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/4/213>.

DISCUSSION

Clinical Course and Management

The patient's fractional excretion of sodium was 0.2%, and, therefore, her acute kidney injury and hypernatremia were thought to be consistent with dehydration and a prerenal state. Both resolved with appropriate fluid resuscitation. An otorhinolaryngologist performed a bedside nasal endoscopy and laryngoscopy, which revealed thick yellow mucus in the posterior oropharynx. Repeated GAS rapid testing as well as serum Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus serologies were within normal limits. A multipathogen throat culture and specific cultures for gonorrhea and chlamydia were sent to the laboratory. Thayer-Martin culture grew gram-negative diplococci consistent with *Neisseria gonorrhoeae*. On repeated sexual history the patient disclosed having unprotected receptive oral sex with a 15-year-old male partner 4 weeks earlier. She received appropriate treatment with ceftriaxone and azithromycin and experienced a full recovery.

The Condition

Neisseria gonorrhoeae is a gram-negative diplococci more commonly known to cause cervicitis in females and urethritis in males as well as disseminated disease in both sexes characterized by fever, arthritis, tenosynovitis, and dermatitis. *Neisseria gonorrhoeae* is a rare (1%–2%) (1)(2) cause of pharyngitis that should be considered in a patient with pharyngitis after receptive oral sex. Changes in sexual practices and age of sexual debut are likely to make this diagnosis increasing relevant to frontline pediatric providers.

Most patients with pharyngeal *N gonorrhoeae* are asymptomatic. In fact, in the sentinel study of pharyngeal gonococcal infection conducted in a very high-risk population, pharyngeal *N gonorrhoeae* was not significantly more prevalent in those with sore throat compared with asymptomatic peers. (3) These data raise the question of whether *N gonorrhoeae* is pathologic or simply an incidental finding in patients with pharyngitis of a different etiology. Our patient's presentation and improvement with appropriate treatment suggest that it is in fact pathologic; however, additional research is needed to clarify the relationship between *N gonorrhoeae* and sore throat. Based primarily on case reports, when symptomatic, the clinical presentation of *N gonorrhoeae* pharyngitis varies widely, ranging from acute suppurative tonsillitis, to subacute mild pharyngitis, often with adenopathy, and usually without fever. (3)(4)(5)

Diagnosis

Given the variability in clinical presentation, suspicion based on symptoms alone is difficult, and epidemiologic clues should be used. The practice of receptive oral sex is the method of infection. Historically, rates are highest in men who have sex with men, followed by females, and lowest in men who do not have sex with men. (3)(6)(7) In addition, patients with urogenital gonorrhea are at increased risk for concurrent pharyngeal infection. (7) The percentage of youth reporting to have had sexual intercourse is decreasing. (8) However, younger birth cohorts are more likely to report oral sex during adolescence, indicating that the rate of oral sex during adolescence is rising. (9)

Risk stratification is limited by the ability to accurately ascertain sexual practices. Studies have found that patients underreport oral sexual exposures to health-care providers. (10) In addition, a minority of adolescent patients (20%) consider oral-genital contact to be sex and, therefore, many may not disclose such practices when asked generally about sexual history. (11) This was the case for this patient and likely contributed to her delay in diagnosis. Therefore, relevant sexual exposures should be explicitly discussed.

Standard throat culture will not identify *N gonorrhoeae*. When gonococcal pharyngitis is suspected, clinicians should contact their laboratory such that specific testing can be pursued. Traditionally, culture on Thayer-Martin medium has been used to diagnose gonococcal pharyngitis. However, nucleic acid amplification testing is more sensitive than culture on Thayer-Martin medium (95% versus 47%), with similar specificity (98% versus 100%). (12)

Treatment

Pharyngeal gonococcus is more likely to fail therapy than urogenital disease. Decreased antibiotic penetrance into the pharynx and horizontal gene transfer of resistance genes from commensal oral *Neisseria* species have been proposed as possible explanations. (13) The Centers for Disease Control and Prevention (CDC) recommends single doses of intramuscular ceftriaxone (250 mg) and oral azithromycin (1 g) for treatment of gonococcal pharyngitis. (14) Azithromycin serves to prevent the emergence of cephalosporin-resistant *N gonorrhoeae* and to treat possible *Chlamydia trachomatis* coinfection. (14)

Lessons for the Clinician

- *Neisseria gonorrhoeae* is a rare but not insignificant cause of pharyngitis.

- Clinicians should consider the diagnosis in high-risk populations or cases of pharyngitis in which other common causes have been excluded.
- Diagnosis can be made by nucleic acid amplification testing of a pharyngeal swab.
- Recommended treatment is 1 dose of intramuscular ceftriaxone (250 mg) and 1 dose of oral azithromycin (1 g).

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Case 3: Persistent Pharyngitis in a 14-year-old Girl

Conor O'Halloran and Ariel Winn

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3 Persistent Respiratory Distress in a Teenager Treated for Severe Asthma Exacerbation

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AUTHOR DISCLOSURE Drs Shieh and Siddaiah have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 15-year-old girl with severe persistent asthma presents to the emergency department with acute respiratory distress. Her common triggers are environmental allergens, predominantly dogs and cats. Her asthma had been fairly controlled with her current home regimen, which included daily fluticasone/salmeterol 230/21 μg 2 puffs twice daily, montelukast 5 mg once daily, loratadine, and as-needed albuterol until she was recently exposed to dogs. She experiences a cough, becomes dyspneic, and uses her rescue inhalers, which fail to provide relief.

On presentation, her vital signs are significant for a heart rate of 124 beats/min and a respiratory rate of 28 breaths/min. She requires oxygen therapy to achieve oxygen saturation of 98%. The physical examination reveals that she is leaning forward in the tripod position and using accessory muscles to breathe. She is unable to speak full sentences without feeling short of breath. Her lungs have significantly decreased breath sounds, with occasional wheezing heard throughout her lung fields. No stridor is present. There is no cyanosis in her extremities. A portable chest radiograph reveals hyperexpansion with prominent central lung markings and peribronchial cuffing consistent with reactive airway disease.

She is immediately treated with subcutaneous epinephrine, nebulized albuterol, nebulized ipratropium, and intravenous methylprednisolone. Because of poor response, she receives intravenous magnesium sulfate and intravenous aminophylline. Results of polymerase chain reaction testing for nine common viral respiratory pathogens are negative. Due to increasing dyspnea requiring oxygen therapy, she is transferred to the ICU, where she requires treatment with continuous albuterol and systemic corticosteroids. On day 3, she no longer requires continuous albuterol. Due to intermittent respiratory distress with poor air movement and stridor, she is treated with continuous albuterol and heliox on day 6. A minimally invasive bedside tool confirms her diagnosis, and she is discharged 2 days later.

The Case Discussion, References, and Suggested Readings appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/5/261>.

DISCUSSION

According to the National Institutes of Health, (1) treatment for an asthma exacerbation should be initiated immediately. Supplemental oxygen should be started to correct hypoxemia. Patients should be treated with repetitive or continuous short-acting β_2 -agonist with the addition of inhaled ipratropium bromide in severe cases. Oral corticosteroids should be given to patients with moderate or severe exacerbations or patients who fail to respond to initial treatment to reduce airway inflammation. Adjunctive treatments, such as intravenous magnesium sulfate or heliox, should be considered in patients who are unresponsive to treatment. Response to treatment can be monitored with pulse oximetry, clinical symptoms, and physical examination.

Differential Diagnosis

If a patient with presumed asthma exacerbation does not respond to bronchodilator treatment, alternative diagnoses must be considered. Patients with anaphylaxis present with respiratory distress and frequently have skin findings, including flushing, urticaria, and angioedema. Epiglottitis is characterized by an abrupt onset of high fever, with drooling, dysphagia, and sore throat. Patients with airway compromise due to foreign body obstruction present with tachypnea, tachycardia, or stridor. These patients may rapidly deteriorate if swelling or bleeding occurs in the airway. Patients with laryngeal abnormalities, including polyps or cysts, causing obstruction have symptoms such as hoarseness, change in voice quality, and increased effort in voice production.

The Condition

Vocal cord dysfunction (VCD), also known as paradoxical vocal fold motion, can mimic an asthma exacerbation. The incidence of VCD in pediatric patients is unknown. However, the study by Powell et al (2) reported that VCD mainly affects adolescents and is more prevalent in girls. It is believed to have similar triggers as asthma, including cold air, allergies, and exercise. Other triggers for VCD include viral upper respiratory tract infections, gastroesophageal reflux disease, or psychological stresses. Patients with VCD may experience dyspnea, tightness in the throat, or non-productive cough. Stridor may be heard and is usually loudest in the anterior neck. It is difficult to distinguish VCD from asthma because both conditions have similar symptoms, and patients may actually have both conditions.

Diagnosis

To definitively diagnose VCD, direct visualization through a laryngoscope of inappropriate adduction of the vocal cords

with posterior chinking during inspiration or both inspiration and expiration is required. As a result of this obstruction, the patient experiences wheezing or stridor over the larynx, which can be conducted to the lower lung fields. It is difficult to diagnose VCD in an asymptomatic patient because the vocal cords show normal movement, and most patients will have normal pulmonary function studies. However, when symptomatic, patients in a report by Niggemann et al (3) had a truncated inspiratory segment with blunting of the expiratory limb of flow volume curves. A normal flow volume curve in a symptomatic patient does not rule out VCD. Occasionally, symptoms can be triggered during an exercise challenge study, methacholine challenge study, or hyperventilation.

After a prolonged hospital course, slow clinical improvement with intermittent stridor, and poor response to albuterol, a bedside examination with a flexible fiberoptic laryngoscope is performed on this patient, which reveals paradoxical vocal cord movement during hyperventilation.

Management

The goal of immediate treatment is to stop the attack. Breathing techniques to relax the throat or exhaling through pursed lips helps counteract the closure of the respiratory tract. Some techniques to open vocal cords include panting with the tongue extruded, diaphragmatic breathing, and taking rapid deep inspirations. In severe cases, positive pressure ventilation forces air through the narrowed opening formed by the adducted cords. Previous reports, such as that by Reisner and Borish, (4) demonstrate that a mixture of helium and oxygen (heliox) is effective in relieving symptoms. Endotracheal intubation or permanent tracheostomies may be required in severe cases.

The mainstay for long-term management of VCD includes laryngeal control therapy and psychotherapy during asymptomatic periods. Such speech therapy includes techniques for voice control, sip and swallow routines, and breathing exercises that use the diaphragm to relax the vocal cords. Concurrently, psychotherapies have been used to reduce stress and anxiety. In a study of adults by Varney et al, (5) insomnia, anxiety, and stress were associated with VCD, and low-dose amitriptyline was shown to be effective to treat patients. Patients should remain aware of precipitating triggers and identify onset of symptoms quickly. Other triggers of asthma should be controlled to minimize a component of a reactive airway.

Clinical Course

She was treated with heliox, and her symptoms improved significantly. The following exercises were used to relax the vocal cords and focus on diaphragmatic breathing:

- Place a book on the abdomen to increase awareness of abdominal movement while breathing.
- Sniff in through the nose slowly and gently exhale through pursed lips.
- Make the *s* or *sh* sound during exhalation.
- Inhale and exhale deeply and slowly.
- Pant quickly in and out of the nose to feel movement of the diaphragm.

She was discharged, and no adjustments were made to her home medications.

Lessons for the Clinician

- An astute clinician must consider vocal cord dysfunction (VCD) in patients who do not show response to nebulized treatment or who require multiple hospital visits despite taking large doses of medications for asthma.
- Diagnosis of VCD is confirmed by visualization of adduction or posterior chinking of vocal cords through a fiberoptic laryngoscope.
- Breathing techniques to relax the throat or counteract the closure of the vocal cords is effective to manage VCD, and positive pressure ventilation with heliox is effective in severe cases.
- Speech therapy is effective for long-term management of VCD to relax the vocal cords.
- In patients with VCD and underlying asthma, proper diagnosis of VCD can decrease exposure to inhaled corticosteroids, reduce unnecessary adjustments to medications, and reduce adverse effects from systemic therapy.

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Case 3: Persistent Respiratory Distress in a Teenager Treated for Severe Asthma Exacerbation

Andrew Shieh and Roopa Siddaiah

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Pediatrics in Review

An Official Journal of the American Academy of Pediatrics

Case 3: Persistent Respiratory Distress in a Teenager Treated for Severe Asthma Exacerbation

Andrew Shieh and Roopa Siddaiah

Pediatrics in Review 2018;39;261

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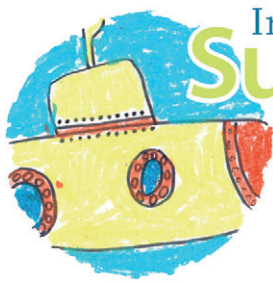
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Index of Suspicion

4

Poor Feeding and Lethargy in a 32-day-old Infant

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AUTHOR DISCLOSURE Drs Peebles, VanHooren, Gunz, and Salvadori have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 32-day-old boy presents to the emergency department with a 12-hour history of poor feeding and lethargy. The child was born at 34+1 weeks and spent 2 weeks in the NICU, where he was fed infant ready-made formula by gavage feeding as he gradually increased his suckling. He was discharged 5 days before his presentation.

On assessment, he is noted to be pale, hypotonic, and irritable. He is hypothermic, with a rectal temperature of 97.0°F (36.1°C). His heart rate is 150 beats/min, and capillary refill is noted to be appropriate.

A full sepsis evaluation is performed. White blood cell count is 20,000/ μ L (20×10^9 /L), hemoglobin is 9.3 g/dL (93 g/L), and platelet count is 63×10^3 / μ L (63×10^9 /L). Cerebrospinal fluid analysis shows a white blood cell count of 10,000/ μ L (10×10^9 /L), a protein level of 1,650 g/dL (16,500 g/L), and a glucose level of 5.6 mg/dL (0.31 mmol/L). He is started on ampicillin, cefotaxime, and acyclovir. Within 5 hours of admission, he becomes mottled and tachycardic (190 beats/min), with intermittent apneas requiring PICU admission. Gram-negative bacilli are identified on gram stain in the cerebrospinal fluid (CSF) 6 hours after presentation; the acyclovir is stopped, and the antibiotics are changed to meropenem.

The Case Discussion and Suggested Readings appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/2/95>.

DISCUSSION

The organism isolated from blood and CSF on the day of admission was *Cronobacter sakazakii*.

Any neonate presenting with fever or hypothermia should undergo a full sepsis evaluation, including a lumbar puncture. The most common bacteria causing sepsis and meningitis in the neonatal age group are group B *Streptococcus*, *Escherichia coli*, and *Listeria monocytogenes*. Appropriate empirical antibiotics for presumed sepsis in neonates include ampicillin and cefotaxime. In cases in which an infant worsens on standard therapy, when the infant is seriously ill and standard therapy has been considered, or when a resistant gram-negative organism is isolated, therapy can be changed to meropenem. In our institution, use of meropenem mandates an infectious disease consultation.

Brain abscess is a rare complication of meningitis and is more common in premature or immunocompromised infants. In neonates, gram-negative species predominate as causative organisms, and *Enterobacteriaceae*, *Citrobacter* species, *Serratia marcescens*, *Proteus mirabilis*, and *Pseudomonas aeruginosa* have been reported. There are case reports of *Staphylococcus aureus* and *Clostridium septicum* causing brain abscesses. The presentation of a brain abscess can be nonspecific and include fever, irritability, temperature instability, apneas, and seizures. The differential diagnosis is broad and includes infectious etiologies such as meningitis, encephalitis, and subdural/epidural empyema as well as noninfectious etiologies such as neoplasms, intracranial hemorrhages, strokes, and toxic ingestions. Imaging studies are, therefore, paramount in making the diagnosis and should be performed on all neonates diagnosed as having gram-negative meningitis.

The most sensitive imaging modality for diagnosing brain abscesses is MRI. Brain abscess appears as a ring-enhancing lesion on MRI. Findings from MRI early in the course can be nonspecific, with high T2-weighted signal intensity; however, as the abscess forms, MRI reveals a ring-enhancing lesion. Diffusion-weighted imaging and magnetic resonance spectroscopy can help distinguish pyogenic abscesses from other ring-enhancing lesions such as tumors or tubercular abscesses.

The Condition

Cronobacter species are gram-negative bacteria that form a newly defined genus, formerly *Enterobacter sakazakii*. Neonatal infections with *Cronobacter* species are rare, with less than 150 cases ever reported globally in infants up to 2 months of age. Severe disease manifestations include meningitis, bacteremia, and necrotizing enterocolitis. Neonatal

meningitis due to *Cronobacter* is associated with a high prevalence of brain abscess, cyst formation, infarctions, a high mortality rate (40%–80%), and long-term neurologic sequelae in survivors. Whenever *C sakazakii* is isolated from neonatal blood or CSF, serial MRIs should be performed to evaluate for abscess formation and guide optimal management. Infants at greatest risk include those who are preterm, low birth-weight (<2,500 g), or immunocompromised.

Neonatal infections with *C sakazakii* have been linked to powdered formulas, including infant formulas, follow-up formulas, and human milk fortifier. Manufacturing methods used today to produce powdered formula do not produce sterile formula, and inappropriate handling practices can exacerbate this. Health organizations have advised against feeding powdered formula to premature or immunocompromised babies because of the risk of *C sakazakii* and other bacterial infections. Contamination can take place at the source (contaminated raw materials or manufacturing surfaces) or at home (contaminated preparation surfaces, water, or bottles). In recognition of the risks posed by contaminated powdered infant formula, the World Health Organization has issued guidelines for the preparation of powdered formula in health-care settings and at home. These stress the importance of hand washing and sterilization of equipment, preparing formula with boiled water, and feeding formula immediately (once cooled) or refrigerating promptly for use within 24 hours.

It is important for pediatricians to be aware of this infection because it often has devastating outcomes and for infants at greatest risk (ie, those in NICUs) is the rationale behind many recommendations regarding infant feeding practices, especially in hospitals.

Patient Course

On day 4 of admission he had a generalized tonic-clonic seizure and was loaded with phenobarbital. He underwent MRI, which showed generalized edema and restricted diffusion of the left cerebral hemisphere with asymmetric mass effect. On day 14, he became increasingly lethargic. An urgent computed tomographic scan of his head showed a large cerebral abscess in the left cerebral hemisphere causing significant mass effect with brainstem distortion (Fig). A therapeutic ventricular tap was performed. The CSF was again purulent (white blood cell count, 5,000/μL [5×10^9 /L]; protein level, 1,455 g/dL [14,550 g/L]; and glucose level, 5.6 mg/dL [0.31 mmol/L]). Based on worsening neurologic status despite maximal therapy, his poor prognosis was discussed with his parents and a course of palliation was begun. The child died 4 days later. On review of this infant's feeding history, no breaches of infection control practice or exposure to powdered formula could be ascertained.

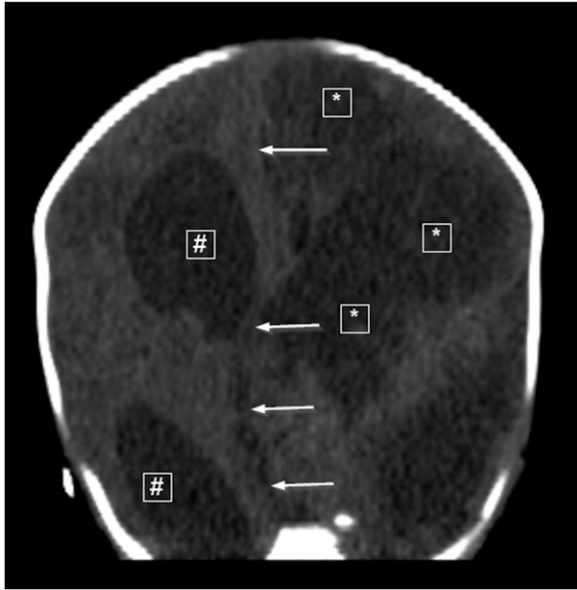


Figure. Computed tomographic scan of the head demonstrating a large fluid collection with irregular margins in the left cerebral hemisphere consistent with cerebral abscess (*). The abscess is noted to be causing significant mass effect with midline shift (arrows) causing secondary compression of the ventricular system with evidence of ventricular dilation over the right hemisphere (#).

Lessons for the Clinician

- *Cronobacter sakazakii* is a rare cause of devastating neonatal infections.

- Powdered infant formula is not sterile, and strict guidelines exist for preparation and storage to minimize the risk of bacterial contamination.
- If alternatives to human milk are necessary, liquid infant formula should be used for infants at greatest risk (ie, those in NICUs).
- Any infant who grows *Cronobacter* species from any sterile site should undergo a full sepsis evaluation (including lumbar puncture) and brain imaging.
- Brain imaging is an important component of therapy and should be performed in all neonates with focal symptoms related to meningitis and in those with certain pathogens, especially *Enterobacteriaceae*. Follow-up imaging should be performed before stopping therapy.

Suggested Readings

- Feeding I. Recommendations for the preparation and handling of powdered infant formula (PIF). <https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/infant-feeding/recommendations-preparation-handling-powdered-infant-formula-infant-feeding.html>. Accessed December 4, 2017
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Case 4: Poor Feeding and Lethargy in a 32-day-old Infant
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3 Priapism in a 13-year-old Boy

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AUTHOR DISCLOSURE Drs Clark, Hsu, Darves-Bornoz, Tanaka, Mason, and Katzenstein have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 13-year-old boy without a significant medical history presents with a painful erection that has persisted for 3 days. He denies any known stimulus, trauma, or new medications. He has not had any other symptoms except for vague headaches and leg pain in the past month. He has seen 2 providers in the past 3 days, who prescribed therapies including lidocaine, oral pseudoephedrine, and antibiotics without relief. No laboratory tests were obtained at either visit.

On physical examination he is afebrile, his blood pressure is 146/76 mm Hg, and his heart rate is 117 beats/min. He appears uncomfortable from penile pain but is nontoxic. On abdominal examination, his spleen is palpable 4 cm below the costal margin, and his genitourinary examination reveals an erect penis that is erythematous, tender to palpation, and without any obvious perfusion defects. The remainder of his examination findings are normal.

Pediatric urology is urgently consulted for management of priapism, and laboratory studies are sent, which reveal the etiology of his symptoms.

DISCUSSION

A complete blood cell (CBC) count reveals a white blood cell (WBC) count of 350,000/ μ L (350×10^9 /L), hemoglobin level of 8.5 g/dL (85 g/L), and platelet count of 450 $\times 10^3$ / μ L (450×10^9 /L). The differential count includes 67% neutrophils, 5% lymphocytes, 2% monocytes, 1% basophils, 13% metamyelocytes, 9% myelocytes, 1% promyelocytes, and 2% blasts (Fig 1). Levels of electrolytes, blood urea nitrogen, creatinine, liver enzymes, and uric acid are all normal. Flow cytometry of the blood shows granulocytosis with no increase in blasts. Priapism secondary to chronic myelogenous leukemia (CML) with leukostasis is diagnosed.

Clinical Course

Urology performed a penile phenylephrine injection, without improvement. The patient was admitted to the PICU for leukapheresis and was started on

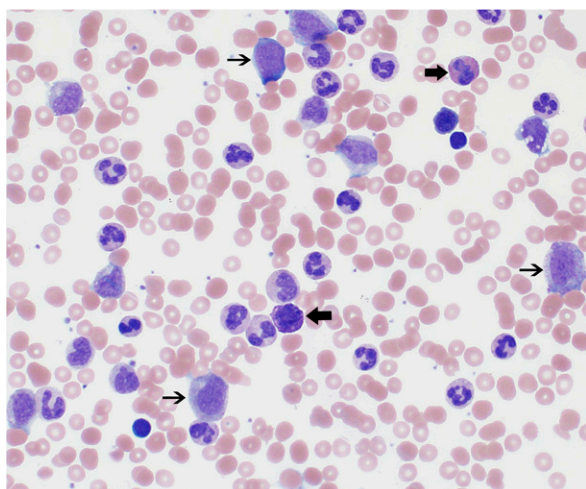


Figure 1. The peripheral blood smear shows a marked leukocytosis consisting predominantly of myeloid elements, including left-shifted myeloid forms (thin arrows) and scattered basophils and eosinophils (thick arrows).

fluids, hydroxyurea, and allopurinol. Leukapheresis was performed with reduction of the posthydration WBC count from $255,000/\mu\text{L}$ ($255 \times 10^9/\text{L}$) to $222,000/\mu\text{L}$ ($222 \times 10^9/\text{L}$). Urology then performed corporeal irrigation twice within 12 hours, both with initial detumescence and nearly immediate return of the erection. Bone marrow biopsy was performed, and cytogenetic studies revealed the Philadelphia chromosome, confirming the diagnosis of CML (Figs 2–4). He was started on imatinib, with further improvement of his leukocytosis. He underwent a third corporeal irrigation with a distal shunt

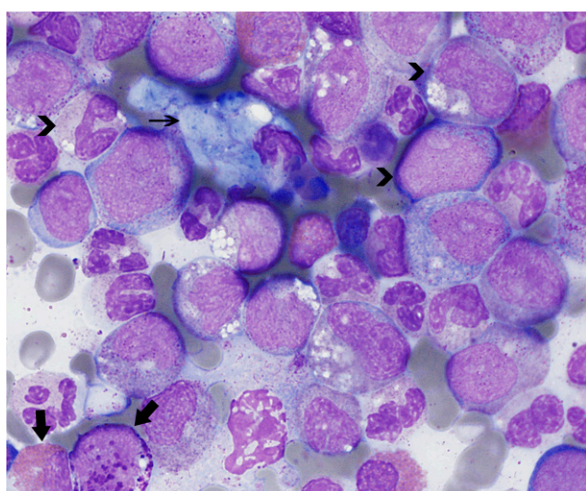


Figure 2. The bone marrow aspirate smear shows myeloid hyperplasia with a full range of maturation (arrowheads) as well as eosinophilia and basophilia (thick arrows) with no increase in blasts. Sea-blue histiocytes (thin arrow) are present. Megakaryocytes (not pictured) include small, hypolobated forms.

procedure 36 hours after the previous irrigation. At the time of hospital discharge, his genitourinary examination was improved but still with some phallus rigidity and tenderness.

The Presenting Condition

Priapism is rare in children but requires urgent intervention. The most common type is ischemic priapism, classified by painful venous occlusion and subsequent tissue ischemia. Much less common is nonischemic priapism, caused by painless high arterial flow fistulization, typically secondary to trauma.

In children presenting with priapism, approximately 65% of cases are attributable to sickle cell disease, and in rare instances, sickle cell trait. Ten percent of cases are secondary to leukemia, 10% are secondary to trauma, 10% are idiopathic, and the remaining 5% are secondary to medications. Of the 10% secondary to leukemia, approximately half are CML.

Management of priapism should involve primary measures of analgesia and attempts to ease the erection with cold packs, urination, ejaculation, and/or physical exercise, along with urgent urologic consultation. Laboratory testing should include a CBC count and electrolytes to assess for common pathologies associated with priapism. When priapism is secondary to an underlying disease process, addressing the primary pathology in addition to performing the necessary urologic procedures is recommended. In patients with sickle cell disease, priapism may be treated with exchange transfusion, although evidence supporting such therapy is sparse. When hyperleukocytosis with leukostasis is present, treatment of the malignancy and/or leukapheresis can be useful in improving symptoms and preventing complications.

Timeliness of care is of utmost importance because ischemic priapism without proper treatment can lead to progressive penile necrosis and fibrosis, with the long-term complication of erectile dysfunction. The likelihood of erectile dysfunction increases with the duration of symptoms. (1)

The Underlying Condition

In children, CML is rare, making up 2% to 3% of all leukemia diagnoses. Its hallmark is the Philadelphia chromosome, an abnormal chromosome 22 that is created by the reciprocal translocation $t(9;22)(q34.1;q11.2)$, which fuses the *ABL* gene on chromosome 9 to the *BCR* gene on chromosome 22. The *BCR-ABL* fusion protein leads to overproduction of granulocytes at all stages of maturation, resulting in marrow replacement. The treatment of CML has been

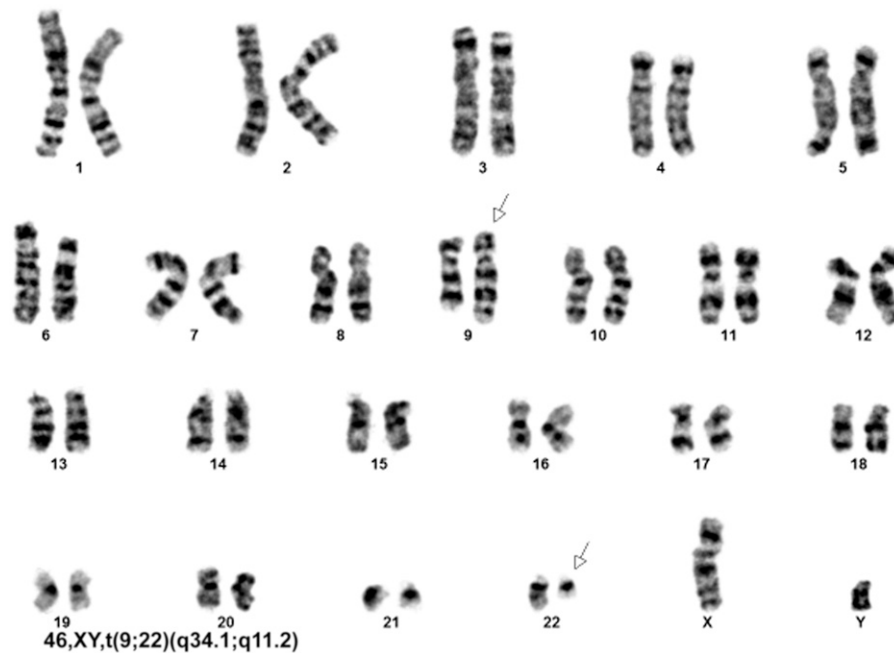


Figure 3. Cytogenetic analysis shows a t(9;22)(q34.1;q11.2) translocation in all 20 cells analyzed. Arrows indicate the abnormal, elongated chromosome 9 (upper arrow) and abnormal, truncated chromosome 22 (lower arrow).

dramatically altered by tyrosine kinase inhibitors (TKIs), which directly inhibit the BCR-ABL fusion protein. Before the use of these targeted agents, stem cell transplant was the only curative option. The optimal length of TKI therapy, the cost analysis of TKI versus stem cell transplant, and the potential consequences of long-term TKI use in children are not completely known.

Children with CML tend to present with elevated WBC counts (median, 225,000/ μ L [225 \times 10⁹/ μ L]) without increased blasts. Other symptoms often include fatigue, weight loss, night sweats, and abdominal pain and swelling from splenomegaly. Approximately 10% of patients present

with signs of leukostasis, which may include vision changes, intraocular hemorrhages, dyspnea/respiratory distress, headache, altered mental status, hearing changes, aseptic osteonecrosis, and priapism.

Evidence is sparse on the utility of leukapheresis in CML, mainly because cases are rare, but it is generally considered for patients with severe symptoms or evidence of end organ dysfunction, including priapism. In this case, there was minimal change in WBC count and priapism after leukapheresis. (2)

Lessons for the Clinician

- Priapism in a child or adolescent is a urologic emergency and should prompt immediate consultation with a pediatric urologist.
- The most common cause of priapism in children is sickle cell disease, but leukemia should always be considered. Therefore, laboratory tests, including a complete blood cell count and electrolytes, are essential for a pediatric patient presenting with priapism, particularly for those without a history of sickle cell disease or trauma.
- Children with leukemia can present with hyperleukocytosis and leukostasis, which are critical illnesses that require prompt intervention to prevent both acute and chronic morbidity.

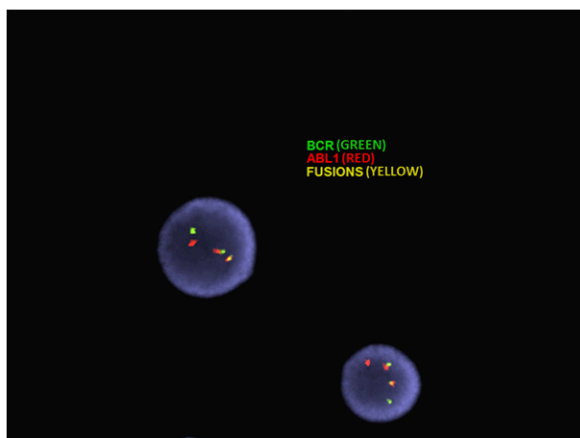


Figure 4. Dual-color–dual-fusion fluorescence in situ hybridization analysis confirms a BCR/ABL1 rearrangement in 95% of analyzed cells.

References for this article are at <http://pedsinreview.aappublications.org/content/39/12/617>.

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3 Progressive Leg Pain and Weakness in a 16-year-old Boy

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PRESENTATION

AUTHOR DISCLOSURE Drs Begley, Briggs, and Williams have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

A 16-year-old boy presents with progressive lower extremity pain and weakness. One month ago, the patient joined the basketball team after living a sedentary lifestyle. Since then, he has developed shin splints and a dull aching pain in his ankles and lower back. He treated the pain with ibuprofen and stretching exercises, resulting in some relief. The day before admission he had severe pain in his hamstrings and also developed lower extremity weakness and numbness during practice. On the morning of admission, his symptoms are too severe for him to be able to walk.

The patient states that his pain is predominantly in his hamstrings and that he feels a “pulling sensation.” He also complains of bilateral numbness and cold sensitivity on his posterior calves and on his feet below the ankles. He recently had coldlike symptoms with no other recent illnesses. He admits to losing 10 lb (4.5 kg) in the past month, which he attributes to participating in daily conditioning exercises. He denies any recent urinary symptoms.

Physical examination reveals a large teenage boy, mildly somnolent from narcotics given for pain. Vital signs show a normal temperature, blood pressure of 130/70 mm Hg, weight of 250.4 lb (113.6 kg), height of 6 feet 6 inches, and BMI of 28.89. Bruises in various stages of healing are present on the lower extremities. Dorsalis pedis pulses are intact bilaterally. Examination of the back reveals mild tenderness to palpation of the lumbar spine; however, he has no paraspinal muscular tenderness, no obvious swelling, and no bruising. Patellar and Achilles reflexes are 2+ bilaterally. No cremasteric reflex or anal tone is performed. Strength for hip flexion is 4/5 bilaterally, knee extension is 5/5 bilaterally, knee flexion is 4/5 bilaterally, ankle plantar flexion is 1/5 bilaterally, and ankle dorsiflexion is 1/5 bilaterally. Sensation to light touch is intact throughout the lower extremities.

Laboratory evaluation shows normal values for complete blood cell count, serum electrolytes, blood urea nitrogen, and creatinine. The serum creatine kinase level is 452 U/L (7.55 μ kat/L) (reference range, 38–176 U/L [0.63–2.94 μ kat/L]) and the C-reactive protein is 0.4 mg/L (3.8 nmol/L).

He is hospitalized for further evaluation.

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/2/94>.

DISCUSSION

Over 48 hours, the patient had progression of his symptoms, with increasing weakness in the distal lower extremities and loss of Achilles reflexes. He also complained of roving numbness, sometimes involving the calves and other times the hamstrings. Because of progressive neurologic findings on examination, a magnetic resonance image (MRI) was ordered.

An MRI of the lumbar spine was initially attempted without sedation, but the patient was unable to tolerate the study secondary to severe radiating bilateral hip pain while lying prone. The MRI was, therefore, performed under sedation and revealed L3-4 disk extrusion with impingement on the cauda equina, as well as hydronephrosis with distended urinary bladder, all consistent with cauda equina syndrome (CES) (Fig). In the postanesthesia care unit after the MRI was performed, he developed urinary retention and inability to void and, therefore, required Foley catheter placement.

The Condition

A rare syndrome, CES develops in 4 to 7 in 10,000 to 100,000 individuals, with disk herniation a cause in 1% to 2% of those cases. (1)(2)(3) Usually CES affects middle-aged men in their 40s and 50s, although trauma-related CES is not age specific. The spinal cord ends at the L1 vertebral level. Below this, the lumbosacral roots form the cauda equina in a common sack, which is responsible for motor

and sensory function in the legs and bladder. Findings are usually consistent with injury to spinal roots rather than the spinal cord. Most injuries at the level of L2 injure the conus medullaris.

Cauda equina syndrome is defined by a loss of function in 2 or more of the 18 nerve roots that compose the cauda equina. Symptoms of CES (1)(2) are low back pain accompanied by radiation of pain into the legs; weakness of plantar flexion of the feet with S1, S2 root involvement, with higher levels leading to weakness in corresponding muscles; bladder and rectal sphincter paralysis with involvement of S3-5 nerve roots; sensory loss in the dermatomal distribution of affected nerve roots; and sexual dysfunction of sudden onset.

Etiologies for CES include epidural tumor or abscess, intervertebral disk herniation, intradural extramedullary tumor, lumbar spine spondylosis, and carcinomatous meningitis. (1)(2)

In our patient, disk herniation caused by a sudden increase in activity/stress resulted in compression of the nerve roots in the lumbar spine.

Diagnosis of CES is difficult because symptoms vary in intensity and evolve slowly over time. (3)(4) In addition, the use of narcotics for pain control can complicate making the correct diagnosis. Diagnosis can be made by a good history and physical examination with appropriate imaging studies, such as computed tomography, MRI, or myelography.

Differential Diagnosis

Spinal tumors, direct trauma, inflammatory conditions such as ankylosing spondylitis, chronic tuberculosis, Guillian Barre syndrome, neuropathy, acute flaccid myelitis, transverse myelitis, and conus medullaris syndrome are some of the conditions that should be considered in a patient with this presentation.

Management

Cauda equina syndrome is considered a neurosurgical emergency because the amount of time before decompression directly affects the recovery of neurologic function, with an increased risk of permanent damage after 48 hours. Bowel and bladder function may take years to recover, but function may continue to improve over a long duration after decompression. Use of corticosteroids is controversial, and more research is needed to ascertain the role of corticosteroids in the management of CES. Left untreated, CES may cause paraplegia.

Patient Course/Management

The patient was transferred to a tertiary care center and taken for emergency L3-4 discectomy with laminectomy



Figure. T2-weighted magnetic resonance image without contrast of the midline sagittal spine showing the disk extrusion at L3-4 and the diffuse disk bulge at L4-5.

by a pediatric neurosurgeon. After the surgery, the patient was transferred to an inpatient pediatric rehabilitation facility. Over 2 months, the patient did have sexual function (per the neurosurgeon) and was able to ambulate with assistance. He still requires intermittent self-catheterization for neurogenic bladder. He also requires numerous medications for persistent neurogenic bowel. The patient was discharged from the hospital with plans for continued intensive outpatient therapy.

Lessons for the Clinician

- Progressing neurologic symptoms need urgent evaluation and reevaluation as the amount of deficit at the time of surgery often dictates the chance of recovery.
- Cauda equina syndrome is considered a neurosurgical emergency.

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Case 3: Progressive Leg Pain and Weakness in a 16-year-old Boy

Amanda Begley, Alicia Briggs and Christopher Williams

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5 Prolonged Fever in a 5-year-old Girl of Myanmese Descent

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AUTHOR DISCLOSURE Dr Bula-Rudas has disclosed no financial relationships relevant to this article. Dr Rathore has disclosed that he serves as principal investigator on research grants from GSK, Gilead Sciences Inc, and Pfizer. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 5-year-old previously healthy girl of Myanmese descent who was born in the United States and has never left the country presents with a 12-day history of high fevers and no other associated signs or symptoms.

On day 5 of fever she was diagnosed as having “the flu” by her pediatrician and was managed symptomatically. On day 9 of the illness she was again evaluated because of persistence of fever. There were no new physical findings. The complete blood cell count and chest radiograph were reported as normal, and a 5-day course of azithromycin was prescribed. There was no specific diagnosis documented in her records for this antibiotic course. She completed 3 days of therapy before hospital admission, and she had no improvement of her fevers.

Because of persistence of fever for 12 days she is hospitalized. Her temperature at the time of admission is 105.8°F (41°C). Physical examination findings are normal except for fussiness. But when observed from outside the room through a window she is calm and comfortable and interacting with her mother.

Laboratory evaluation shows a white blood cell (WBC) count of 12,340/ μ L (12.34×10^9 /L) (75% neutrophils, 18% lymphocytes, and 7% monocytes), a hemoglobin level of 12.4 g/dL (124 g/L), a hematocrit value of 37.4%, and a platelet count of 53×10^3 / μ L. Her erythrocyte sedimentation rate is 49 mm/hour and C-reactive protein level is less than 0.5 mg/dL (<4.8 nmol/L). Serum electrolyte levels are essentially normal except for low carbon dioxide levels of 17 mEq/L (17 mmol/L). Results of polymerase chain reaction (PCR) studies for influenza, respiratory syncytial virus, parainfluenza, adenovirus, and human metapneumovirus are negative. A repeated chest radiograph shows no cardiopulmonary abnormalities. Urine and blood culture are sent and ultimately show no growth. A tuberculin skin test (TST) is nonreactive. The patient continues to spike daily fevers, and her examination results remain unchanged. She remains in the hospital for monitoring of fever and a stepwise approach to evaluate the cause of her fevers. A variety of tests and imaging studies are performed to rule out infectious diseases.

On day 19 of the illness (day 7 of the admission) she becomes encephalopathic. A computed tomographic (CT) scan of the head without contrast is normal. Cerebrospinal fluid (CSF) has a WBC count of 150/ μ L (0.15×10^9 /L) (85% lymphocytes, 5% neutrophils, and 10% monocytes) and a red blood cell count of 4/ μ L (0.04×10^9 /L). Her CSF glucose level is 23 mg/dL (1.28 mmol/L), with a

blood glucose level of 120 mg/dL (6.66 mmol/L) and a protein level of 0.118 g/dL (1.18 g/L). Findings from CSF Gram-stain and acid-fast bacilli (AFB) smear are negative. Results of herpes simplex virus and enterovirus PCR in the CSF are also negative. Magnetic resonance imaging (MRI) of the brain with contrast shows multifocal areas of hyperintense flair signal and restricted diffusion suggestive of

encephalitis. There is no evidence of cerebral abscess. She develops seizures and is transferred to the ICU. On day 20 of the illness, a blood test result is reported to be positive.

The Case Discussion and Suggested Readings appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/2/96>.

DISCUSSION

An interferon- γ release assay (IGRA) for tuberculosis (TB) was reported to be positive and helped us establish a diagnosis of TB meningitis.

The diagnosis of TB meningitis in children is challenging and requires a high index of suspicion. The evaluation of this child with fever of unknown origin warranted a comprehensive laboratory evaluation that included a TB test. The differential diagnosis of prolonged fever includes malignancies, autoimmune diseases, and infections. Being that infections are the most common cause of fever of unknown origin in children, we initiated an evaluation for an infectious etiology. The mother denied having pets at home or contact with animals. Monospot for Epstein-Barr virus, *Bartonella* serology, and human immunodeficiency virus antigen/antibody were negative. Sinus CT, total abdominal ultrasonography, and echocardiography were performed, and all the results were normal. The only abnormal sign in this child was the fever, and not until day 19 of the illness did she become encephalopathic. The CSF analysis raised the suspicion for TB meningitis; therefore, anti-TB treatment with rifampin, isoniazid, pyrazinamide, and amikacin was started, along with corticosteroids. At this time the TST was nonreactive and the IGRA was pending. The IGRA was sent around the same time of TST placement. This child's parents are immigrants from Myanmar. The mother denied exposure to TB on several occasions to several physicians. When the IGRA was reported positive, she then disclosed a close contact of the family as having active TB currently on treatment. The mother reported that she was afraid of disclosing this contact because of fear for this person losing his or her job in a supermarket. There was also a language barrier when interviewing the mother. A live interpreter was used at the time of admission and for the infectious diseases initial interview, but a telephone service interpreter line was used for subsequent visits. The child did not speak English.

The Condition

Tuberculous meningitis accounts for high morbidity and mortality rates in the pediatric population, especially in infants and young children. Children aged 6 months to 4 years are most commonly affected. Diagnosing TB meningitis is challenging in all age groups. The clinical features can appear rapidly or gradually. Infants and young children present more commonly with rapid progression. Involvement of the central nervous system (CNS) occurs either from a renewed activity of an early established caseous lesion in the cerebral cortex or meninges or from direct invasion that occurs during dissemination. The basilar area

of the brain is most commonly affected. Basilar meningitis is common and frequently leads to communication hydrocephalus. Basilar meningitis may also contribute to cranial nerve palsies involving cranial nerves III, VI, and VII. Involvement of the blood vessels may lead to vasculitis and cerebral infarction. Children can present with subtle signs such as low-grade fevers, malaise, irritability, and anorexia. Neurologic signs are usually not present in the early stages of the illness and may not become evident until there are focal deficits, behavioral changes, or comatose appearance. Seizures are more common in children than in adults. To categorize children with TB meningitis, a staging system has been used since the 1960s. This 3-stage system is based on neurologic findings. In stage I there are non-specific signs and symptoms, and there is no evidence of neurologic involvement; this stage can last up to 2 weeks. Stage II is characterized by more abrupt changes, and 2 scenarios can occur: change in the sensorium with or without focal neurologic signs, or no change in the sensorium but focal neurologic deficit. Stage III presents with more devastating signs, such as coma, decorticate posturing, and abnormalities of vital signs, which can progress to death.

Diagnosis

For diagnosing any form of TB, both the TST and the IGRA have many limitations, particularly in children. The TST placement and interpretation are difficult. The IGRAs are easy to obtain and are more specific than the TST, but interpretation has not been well established in younger children. The IGRAs measure ex vivo interferon- γ production from T lymphocytes in response to stimulation with antigens specific to the *Mycobacterium tuberculosis* complex (*M. tuberculosis* and *Mycobacterium bovis*). The IGRAs are reliable in children 5 years and older. Routine testing with both TST and IGRA is not recommended. However, sensitivity to diagnose TB increases when both TST and IGRAs are performed together. Using both also increases the rate of positive results in patients at high risk for TB. The IGRAs have been reported to be more specific than TST in children despite all the limitations. The IGRAs have higher specificity than TST when a child had been immunized with bacillus Calmette-Guérin because they do not test for antigens included in this vaccine.

The diagnosis of TB meningitis is usually suspected once neurologic signs appear. The CSF profile can help with the diagnosis. The presence of lymphocyte-predominant pleocytosis (WBC count, 100–500/ μ L [0.10 – 0.50×10^9 /L]), elevated protein levels (0.100–0.500 g/dL [1.00 – 5.00 g/L]), and low glucose levels (usually ≤ 45 mg/dL [≤ 2.5 mmol/L])

suggest TB meningitis. Sometimes protein levels in the CSF are greater than 0.400 g/dL (>4.00 g/L). A single CSF sample has low sensitivity (20%–40%) for detecting AFB in the smear. Higher volumes of CSF increase the yield for AFB detection. The AFB culture can take several weeks, and sensitivity is low as well (40%–80%). Nucleic acid amplification assays in the CSF have specificity of 98%, although overall sensitivity is approximately 56%.

Both CT scans and MRIs can show pathologic changes of TB meningitis and may provide important information for prognosis as well as diagnose complications of TB meningitis. Basal enhancement, hydrocephalus, tuberculoma, and infarction are findings more commonly seen in CT scans of children with TB meningitis, whereas subdural collections are more common in those with pyogenic meningitis. Recent data suggest that precontrast hyperdensity in the basal cisterns is the most specific radiologic sign of TB meningitis in children.

Treatment and Prognosis

Treatment of TB meningitis in children is still controversial. The American Academy of Pediatrics recommends the use of 4 drugs: rifampin, isoniazid, pyrazinamide, and ethionamide or an aminoglycoside. Once susceptibilities are determined, the ethionamide or the aminoglycoside can be discontinued. Pyrazinamide and ethionamide or an aminoglycoside are given for 2 months, and rifampin and isoniazid are given for 9 to 12 months. The use of adjunctive corticosteroids is definitively recommended in children. Corticosteroids reduce mortality but not morbidity. Diagnosing TB meningitis in the earlier stages is important for preventing the associated neurologic morbidity. The prognosis is poor when the diagnosis is made in stage III.

Patient Course

The patient's neurologic status deteriorated. She remained comatose with decorticate posture. The CSF culture grew

M tuberculosis after 1 month of incubation, and it was confirmed by PCR. She was transferred to a rehabilitation facility and was discharged after completion of an assessment for establishing a long-term plan for care of a medically complex patient with a poor neurologic prognosis.

Lessons for the Clinician

- Evaluation of fever of unknown origin should follow a tiered approach.
- Pulmonary and extrapulmonary tuberculosis (TB) should be considered in the differential diagnosis of fever of unknown origin in children.
- Both a tuberculin skin test and an interferon- γ release assay (IGRA) increase the positive predictive value when used in combination in children at higher risk for TB.
- Conducting a complete TB screening questionnaire is very important in any child with risks for TB infection.
- A positive IGRA result in an infant or young child likely indicates infection with *Mycobacterium tuberculosis*, but a negative result does not rule it out.

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2 Rapid Growth and Abnormal Menstrual Bleeding in a 17-year-old Girl

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AUTHOR DISCLOSURE Drs Senguttuvan, Chin, Elrokhsi, and Wheeler have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 17-year-old girl presents for concerns of growing too fast and having continuous menstrual bleeding for the past 4 months. Per her adoptive mother, she has been growing fast since the beginning of adolescence and is continuing to grow taller. Four months before her visit, she began having excessive and continuous menstrual bleeding. She was seen by a gynecologist a month before the current visit and was started on an oral contraceptive pill. However, her menstrual bleeding continues. She reports no visual disturbances, headaches, nausea, vomiting, weakness or numbness in the upper/lower extremities, or galactorrhea. On review of her records, her height has been at greater than the 97th percentile since 11 years of age (Fig 1). Her medical history is significant for mild scoliosis, sleep apnea, and anemia, as well as tonsillectomy and adenoidectomy at 16 years of age. Her social history is complicated by the early death of her biological mother and a history of mental illness in both biological parents.

Her vital signs are as follows: heart rate, 76 beats/min; blood pressure, 131/76 mm Hg; and temperature, 97.3°F (36.3°C). Physical examination is remarkable for tall stature (height, >97%; Z = +3.90 SD above the mean) and obesity (body mass index >97%, Z = +2.43 SD above the mean), coarse facial features, and very large hands and feet. She also has soft puffy palms. No gross visual field defects are noted. Fundus examination results are normal. Results of the remaining neurologic examination are normal.

The patient had brain magnetic resonance imaging (MRI) without contrast performed at an outside institution that reported a sellar mass with suprasellar extension, consistent with either a pituitary macroadenoma versus craniopharyngioma measuring 2.6 × 2.3 × 2.1 cm (Fig 2).

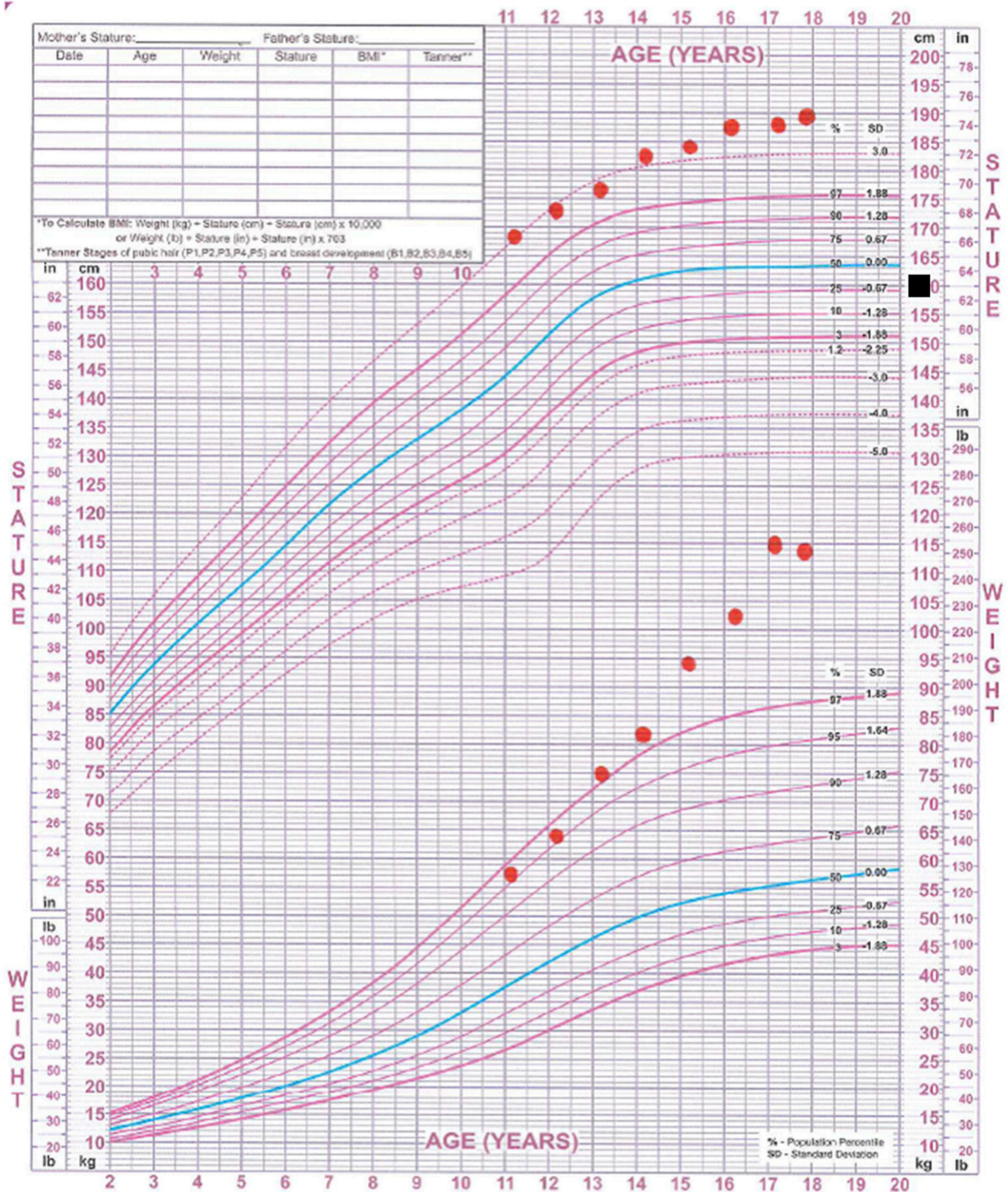


Figure 1. Growth charts show that the height has been at greater than the 97th percentile since 11 years of age and that weight followed the trend after 13 years of age. Black box = mid-parental height.

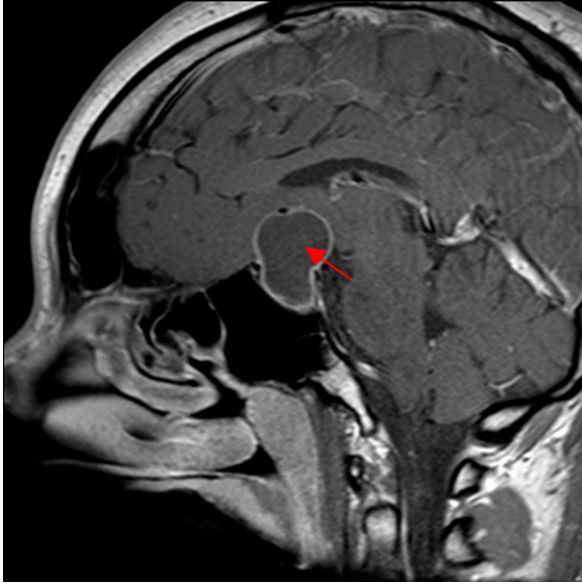


Figure 2. Magnetic resonance image of the brain shows a sellar mass (arrow) with suprasellar extension, consistent with either a pituitary macroadenoma or craniopharyngioma.

DISCUSSION

Laboratory evaluation showed an increased insulinlike growth factor-1 (IGF-1) level of 893 ng/mL (117 nmol/L) (reference range, 268–430 ng/mL [35–56 nmol/L]). A 2-hour oral glucose challenge (75 g of glucose) did not suppress the GH level to less than 1 ng/mL (<1 mg/L). Her serum growth hormone (GH) level was 10.9 ng/mL (10.9 mg/L) (reference range, <1 ng/mL [<1 mg/L]), consistent with GH excess. She also had a low free thyroxine level with a normal thyrotropin level, suggestive of central hypothyroidism. Her prolactin level was increased at 68.4 ng/mL [68.4 µg/L] (reference range, 2.8–26.0 ng/mL [2.8–26 µg/L]). Her cortisol level was 16.2 µg/dL (447 nmol/L) (reference range, 2.3–23.3 µg/dL [63–643 nmol/L]). The luteinizing hormone (<0.1 mIU/mL [<0.1 IU/L]) and follicle-stimulating hormone (FSH) (<0.3 mIU/mL [<0.3 IU/L]) levels were suppressed because she was taking an oral contraceptive pill.

Differential Diagnosis

In children, the differential diagnosis for overgrowth syndromes includes Sotos syndrome, Beckwith-Wiedemann syndrome, Perlman syndrome, Simpson-Golabi-Behmel syndrome, Weaver syndrome, and Marshall-Smith syndrome. The patient's clinical presentation, timing of onset of symptoms, laboratory test results, and brain MRI findings were all consistent with a diagnosis of gigantism caused by GH excess due to the sellar mass.

The Condition

Giants have been a subject of fascination throughout history. From the Biblical accounts of Goliath to the more contemporary Robert Wadlow (Alton giant) and Andre the Giant, giants have been a topic of interest through the ages. Gigantism refers to GH excess that occurs during childhood when the epiphyseal growth plates are open, allowing for excessive linear growth, whereas acromegaly indicates the same phenomenon occurring after epiphyseal growth plate closure.

The incidence of acromegaly is calculated at 3 to 4 cases per million per year, whereas gigantism is extremely rare, with approximately 100 reported cases to date. This is likely an underestimate of the true number. Children with pituitary gigantism have extraordinarily rapid linear growth and are frequently obese. However, the rapid growth in height typically precedes weight gain.

Initial screening tests should include evaluation for pituitary function, including IGF-1 and prolactin levels, as well as screening for visual field defects. The gold standard for diagnosing GH excess is the GH suppression test. Serum GH levels measured 2 hours after a glucose load

(1.75 g/kg; maximum, 75 g) fails to suppress to less than 1 ng/mL in cases of GH excess. An MRI of the pituitary gland with contrast is very helpful in locating the source of GH excess.

Management

The 3 therapeutic modalities for pituitary gigantism are surgery, radiation, and pharmacologic therapy. Management of these patients requires a multidisciplinary approach and close follow-up. Pharmacologic therapy includes somatostatin receptor ligands (octreotide, lanreotide) and GH receptor antagonists (pegvisomant).

Ophthalmology evaluation of our patient revealed that she had bitemporal hemianopsia. She was subsequently evaluated by neurosurgery and otolaryngology consultants, and plans were made for surgical excision. The mass was surgically resected via the endonasal route. Her postoperative course was complicated by the development of diabetes insipidus, which presented with large-volume urine output requiring vigorous fluid administration and desmopressin. Histopathology confirmed prolactin- and GH-producing adenoma. Laboratory studies performed 45 days after surgery showed a normal IGF-1 level of 160 ng/mL (21 nmol/L) (reference range, 147–646 ng/mL [19–85 nmol/L]) and a prolactin level of 5.9 ng/mL [5.9 µg/L] (reference range, 4.2–117.9 ng/mL [4.2–117.9 µg/L]). Brain MRI performed 3 months after surgery showed postoperative gliosis and granulation tissue. The patient had irregular menstrual periods due to high prolactin levels. The prolactin levels normalized after surgery, and her menstrual periods became regular at follow-up visits. The patient continues to take desmopressin for diabetes insipidus and levothyroxine for central hypothyroidism and continues to follow up with endocrine, otolaryngology, and neurosurgery specialists.

Lessons for the Clinician

- Children with pituitary gigantism have extraordinarily rapid linear growth and are frequently obese. However, the rapid growth in height typically precedes weight gain.
- Initial screening tests should evaluate for pituitary function, including insulinlike growth factor-1 and prolactin levels. The gold standard for diagnosing growth hormone (GH) excess is the GH suppression test.
- The 3 therapeutic modalities for pituitary gigantism are surgery, radiation, and pharmacologic therapy.
- Clinicians must keep a high level of suspicion for prompt recognition and management of overgrowth syndromes to mitigate the medical and psychological complications of this disease.

NOTE. Portions of this case have been previously published as part of a conference presentation. This case is based on a presentation by Drs Senguttuvan and Elrokhsy at the Endocrine Society's 97th Annual Meeting and Expo, San Diego, California. Poster session: Pediatric Endocrinology, Presentation Date: March 7, 2015 (Poster No. SAT 167).

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4 Recurrent Orange Urine and Abdominal Pain in a 13-year-old Boy

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AUTHOR DISCLOSURE Drs Newman and Kandikattu have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 13-year-old boy presents with acute kidney injury (creatinine level, 5.6 mg/dL [495 μ mol/L]) and hypertension (blood pressure, 133/59 mm Hg). He notes 18 months of recurrent monthly episodes of back and abdominal pain, dark orange discoloration of urine, difficulty voiding, nausea, and anorexia. Most episodes occur the evening or morning after a day playing outside vigorously. His history includes anemia empirically treated with iron since childhood and occasional staring spells not previously investigated. Physical examination reveals an obese white boy without obvious dysmorphic features, abdominal masses, or tenderness and normal neurologic examination findings.

Evaluation reveals elevated serum (12.5 mg/dL [743.6 μ mol/L]) and urine (31.9 mg/dL [1,897.6 μ mol/L]) uric acid levels (fractional excretion, 10.48%) and a low hemoglobin level (9.8 g/dL [98 g/L]) with elevated mean corpuscular volume (93.9 fL), mean corpuscular hemoglobin level (31.3 pg), and reticulocytes (6.7%). Haptoglobin, iron, folate, and vitamin B₁₂ levels are normal. Renal ultrasonography shows no nephrolithiasis. Serum creatine kinase, lactate dehydrogenase, myoglobin, and total porphyrin levels are normal. Urine studies were positive for myoglobin, with normal random calcium levels and calcium to creatinine ratios. The patient is managed with intravenous fluids and started on allopurinol with the concern of elevated uric acid production. Whole exome sequencing confirms the suspected diagnosis.

DISCUSSION

The patient's presentation was suspicious for recurrent exercise-induced rhabdomyolysis, likely secondary to metabolic myopathy. The presence of an elevated uric acid level was unusual, broadening the differential diagnosis to include partial hypoxanthine-guanine phosphoribosyltransferase deficiency or other defects in uric acid metabolism. Whole exome sequencing revealed a de novo substitution (p.S62N) in the *PGK1* gene associated with phosphoglycerate kinase deficiency. A red blood cell enzyme assay confirmed low levels of phosphoglycerate kinase B (<48 U/g hemoglobin; normal values, 165-239 U/g hemoglobin), with elevated levels of quantitative glucose-6-phosphate dehydrogenase (14.3 U/g hemoglobin [0.24 nkat/g hemoglobin]; normal values, 8.8-13.4 U/g hemoglobin [0.15-0.22 nkat/g hemoglobin]) and

pyruvate kinase (16 U/g hemoglobin [0.27 nkat/g hemoglobin]; normal values, 6.7-14.3 U/g hemoglobin [0.11-0.24 nkat/g hemoglobin]).

Phosphoglycerate kinase 1 deficiency is a rare X-linked recessive disorder characterized by hemolytic anemia, myopathy, and neurologic dysfunction (Online Mendelian Inheritance in Man entry 311800). Phosphoglycerate kinase 1 catalyzes the conversion of 1,3-disphosphoglycerate to 3-phosphoglycerate during glycolysis. Clinical presentation includes hemolytic anemia, (1)(2) myopathies, (3) and neurologic involvement. (1)(2)(4)(5) Patients can express any combination of manifestations. Myopathic involvement can be severe, including rhabdomyolysis with subsequent renal failure (6) and several reports of recurrent, exercise-induced myoglobinuria.

(1)(3) Clinician's should be aware of the variable manifestations of phosphoglycerate kinase 1 deficiency and consider this and other metabolic myopathies in patients with unexplained recurrent myoglobinuria.

Lessons for the Clinician

- Metabolic myopathies should be considered in patients with recurrent myoglobinuria.
- Whole exome sequencing can be performed when there is a high index of suspicion, given the number of genes and mutations that can result in metabolic myopathy.

References for this article are at <http://pedsinreview.aappublications.org/content/39/7/370>.

Case 4: Recurrent Orange Urine and Abdominal Pain in a 13-year-old Boy

Josef Newman and Bhavana Kandikattu

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Index of Suspicion

1 Recurrent Pneumonia in a 15-year-old Girl

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EDITOR'S NOTE

We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: <https://mc.manuscriptcentral.com/pir>.

AUTHOR DISCLOSURE Drs Jichlinski, Kilaikode, and Koumbourlis have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy 15-year-old girl presents with a history of back pain, chills, and shortness of breath of 1 day's duration. On examination she is afebrile and well appearing despite mild tachypnea (respiratory rate of 24 breaths/min). Oxyhemoglobin saturation is normal (95%–100%) on room air. On auscultation she has absent sounds in the left lower lung (LLL) fields but normal breath sounds on the right. Initial laboratory tests show a white blood cell count of $13,050/\mu\text{L}$ ($13.05 \times 10^9/\text{L}$), a hemoglobin level of 14.1 g/dL (141 g/L), a hematocrit value of 40.5%, and a platelet count of $226 \times 10^3/\mu\text{L}$ ($226 \times 10^9/\text{L}$). A basic metabolic panel is normal, and lactate dehydrogenase and uric acid levels are within their respective reference ranges. The C-reactive protein level is elevated at 8.56 mg/L (81.53 nmol/L). A chest radiograph (CXR) reveals a large area of consolidative opacity in the left hemithorax (compatible with pneumonia and/or atelectasis) and probable pleural effusion (Fig 1).

Her medical history is notable for a diagnosis of mild asthma and an episode of pneumonia 18 months before presentation, diagnosed clinically without CXR and treated with antibiotics as an outpatient. She was also admitted to the hospital twice with a diagnosis of LLL pneumonia and pleural effusion 7 and 6 months before this admission. She responded promptly to antibiotic therapy, and no other intervention was taken. At a follow-up appointment after the second hospitalization she was well appearing but had decreased breath sounds on the left base. Her pulmonary function test result was consistent with mild to moderate restrictive lung defect. A CXR revealed a residual density in the LLL that was thought to represent the gradual clearing of the previous pneumonia.

The patient is admitted to the hospital for further evaluation and treatment with intravenous antibiotics. Further imaging reveals the diagnosis.

DISCUSSION

Recurrent pneumonia in children is always a cause of concern because it often results from underlying conditions or anatomical abnormalities that can be summarized as follows: 1) immunodeficiencies (genetic or acquired), 2) conditions that promote the accumulation of mucus into the lungs (eg, poorly controlled asthma or cystic fibrosis), 3) conditions that impair the clearance of mucus from the airways

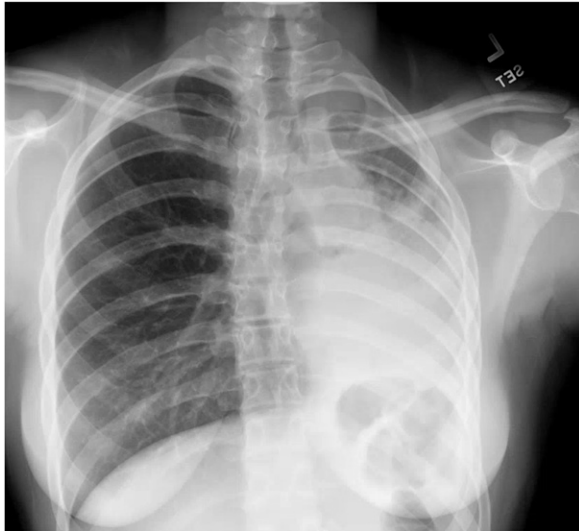


Figure 1. Chest radiograph on hospital admission.

(eg, primary ciliary dyskinesia or tracheobronchomalacia), 4) structural abnormalities of the lungs (eg, cystic pulmonary airway malformations), and 5) indolent infections (eg, tuberculosis).

The patient's CXRs all showed partial consolidation of the LLL that had improved during her follow-up appointment. Recurrent pneumonia in the same location is usually associated with an anatomical abnormality and raises suspicion for pulmonary sequestration.

Although the patient was admitted to the hospital 3 times with the diagnosis of pneumonia with pleural effusion, there were elements of her presentation that made a primary diagnosis of infectious pneumonia less likely. Specifically, she did not have high fever and leukocytosis, and despite the impressive consolidation on CXR she was not hypoxemic, suggesting that there was no acute, severe ventilation/perfusion mismatching.

Chest ultrasonography showed only a small pleural effusion and evidence of collapse versus consolidation of most of the left lung. A computed tomographic (CT) scan of the chest revealed a mass lesion at the origin of the left main bronchus, consolidation and collapse of the left lung, a small circumferential pleural effusion, and marked leftward mediastinal shift (Fig 2).

Flexible bronchoscopy revealed a large, irregular, lobulated, "cauliflower-like" mass at the lower left wall of the trachea that was obstructing the takeoff of the left mainstem bronchus and part of the carina. The mass was soft and fleshy (Fig 3). The right mainstem bronchus and its lobar and segmental bronchi were patent. Multiple forcep biopsies were obtained. Pathologic evaluation revealed large cells with abundant cytoplasm that stained positive for vimentin

and S100, consistent with a benign granular cell tumor. Bronchial washings were obtained and were negative for bacterial, fungal, or viral pathogens. The tuberculin purified protein derivative test result was negative.

The Condition

Granular cell tumors (GCTs) originate from Schwann cells, although the exact pathology leading to their formation is unknown. (1) Lung GCTs are extremely rare, accounting for less than 10% of all GCTs, the incidence of which has been estimated to be 5 cases per million person-years in the general population. The incidence in the pediatric population is significantly lower. (2)(3) Pulmonary GCTs tend to be found in the larger airways at bifurcation sites, with a higher number of reported pediatric cases originating in the larynx. (4) Although most often benign, several cases of malignant GCTs have been reported in adults. (5)

Pathologically, GCTs are composed of polygonal or ovoid cells with large eosinophilic, granular cytoplasm. The nuclei are often small, hyperchromatic, and eccentric, with absent mitosis. S-100 protein, neuron-specific enolase, CD56, and chromogranin are expressed in pulmonary GCTs, consistent with the pathology reported in the present case. (6)

The differential diagnosis for bronchial and tracheal masses is large and includes pulmonary carcinomas, hemangiomas, inflammatory pseudotumors, rhabdomyosarcomas, neurofibromas, and squamous cell carcinomas. (1)(7) Note that pneumonia and/or atelectasis may be the presenting symptom of an endobronchial lesion because the intraluminal mass prevents the clearance of secretions from the airways, thus predisposing the patient to infection. The fact that patients clinically improve with antibiotic therapy often delays diagnosis of the tumor.

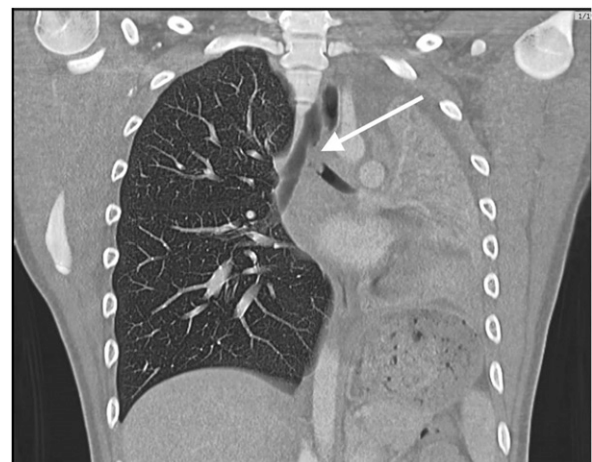


Figure 2. Computed tomographic scan of the chest revealing a filling defect in the left mainstem bronchus, collapse of the left lung, and compensatory hyperinflation of the right lung.

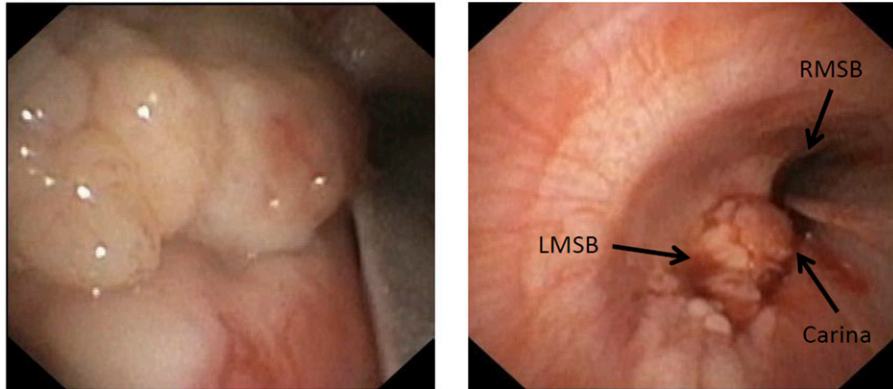


Figure 3. Bronchoscopic appearance of the tumor obstructing the takeoff of the left mainstem bronchus (LMSB), the open right mainstem bronchus (RMSB), and the carina.

Management and Prognosis

Management of GCTs is still debated because few cases have been reported. The tumors do not respond to chemotherapy or radiotherapy, so surgical resection is always necessary. (6) The size of tumors and invasion of the tracheobronchial wall play a role in guiding surgical management; larger, more invasive tumors require complete resection of the lung via thoracic surgery. (8)(9)

Some authors have advocated for endoscopic removal of smaller intraluminal lesions with close follow-up and monitoring for recurrence. (1)(10)(11) Although endoscopy may not always allow the complete resection of the tumor, it is less invasive than pneumonectomy and has significantly lower morbidity. Most importantly, there has never been documented malignancy of a GCT in the pediatric age group, and recurrence due to incomplete resection is rare (0%–12%). (1)(5) However, it must be kept in mind that given the paucity of cases, true recurrence rates remain unknown.

Patient Course

The patient's tachypnea and back pain improved with intravenous antibiotic therapy, and she was discharged on oral antibiotics. The tumor was excised a few weeks later by endoscopic sleeve resection, obviating the need for lobar or total lung resection. The lung fully reexpanded postoperatively.

Conclusion

Our patient's presentation illustrates the need to thoroughly investigate any recurrent or persistent "pneumonia." Because no CT scan or bronchoscopy was performed during the first 2 hospital admissions, we cannot be absolutely certain that the tumor was present at the first admission.

However, the lack of hypoxemia in the setting of absent breath sounds in the LLL field and severe atelectasis on CXRs suggest a slowly growing tumor that was gradually obstructing the LLL, allowing the diversion of the blood flow to the right lung and avoiding the development of ventilation/perfusion mismatching. It is likely that there was also a superimposed infectious process present because the patient clinically improved with the administration of antibiotics during all her hospital admissions. Superimposed bacterial infections are common in endobronchial lesions that impair the clearance of secretions and predispose the affected lung to colonization with bacterial organisms that may cause bacterial bronchitis and/or pneumonia.

Uncomplicated community-acquired pneumonia can be diagnosed and treated on the basis of the clinical presentation and physical findings alone, without the need for CXR. However, when the patient has recurrent episodes, it is virtually impossible to determine whether it is a recurrence of the same pneumonia or a new and unrelated episode. In addition, the radiographic findings of pneumonia may persist for weeks or even months after a single episode. Thus, it is imperative for primary care physicians to follow patients closely and monitor until there is complete clinical resolution. The diagnosis of 2 or more episodes of pneumonia should include CXR and a follow-up CXR several weeks after the clinical recovery to document resolution.

Recurrent or persistent "pneumonia" requires further investigation. A CT scan of the chest with contrast is a reasonable starting point. Suspected pleural effusions should be evaluated with ultrasonography to detect and quantify the presence of free fluid or loculations in the pleural cavity. Flexible bronchoscopy should be performed

when an obstructing lesion is suspected and/or if bronchoalveolar lavage is needed to identify pathogens.

Lessons for the Clinician

- Recurrent pneumonia, especially in the same location, should raise suspicion for an underlying condition predisposing the patient to the pneumonia, and it should be thoroughly investigated.
- Radiographic findings that are disproportionately severe relative to the clinical presentation suggest a chronic, slowly evolving process as opposed to an acute process that is usually associated with substantial distress and hypoxemia.
- Flexible bronchoscopy should be considered when airway obstruction (either from an intraluminal

mass or due to external compression or malacia) is suspected.

- Parapneumonic effusions may be difficult to distinguish from atelectasis/consolidation if there is no free-flowing fluid that would layer in a decubitus position. Thus, their presence should be confirmed by chest ultrasonography and/or computed tomography with contrast.

Note. This case is based on a poster presentation by Drs Kilaikode, Jichlinski, and Koumbourlis at the American Thoracic Society International Conference; Washington, DC; May 22, 2017. Poster No. 8842.

References for this article are at <http://pedsinreview.aappublications.org/content/39/9/464>.



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3 Recurrent Symptom of Sleepiness in an Adolescent Girl

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AUTHOR DISCLOSURE Drs Lambuth, Lantigua, Evangelista, Tchakarov, and Shah have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 17-year-old girl presents with recurrent episodes of sleepiness. Her mother brought her to the emergency department after she was difficult to awaken from sleep. She has had recurrent symptoms of fatigue, difficult arousability, tremulousness, and diaphoresis for 5 months and experiences mild symptoms daily, which are alleviated by eating. In addition, she has had recent weight loss of 4 lb (1.8 kg), headache, and irregular menstruation. The remainder of her medical and family history is normal.

On hospital admission her vital signs are normal. Growth parameters include weight of 103.4 lb (46.9 kg), height of 60 in (152 cm), and BMI of 20.3 (BMI Z-score, -0.3); physical examination findings are normal, and no unusual skin findings are seen. Her initial serum glucose level is 24 mg/dL (1.33 mmol/L), and dextrose-containing intravenous fluids are started. Pediatric endocrinology is consulted to aid in investigation and management.

On further questioning, she reports a previous evaluation in another hospital for these episodes. During her admission she is found to have a fingerstick glucose level of 21 mg/dL (1.17 mmol/L) and receives 2 ampules of dextrose 50% due to recurrent hypoglycemia. She is admitted to the PICU for further monitoring. During a hypoglycemic event, her serum glucose level was 41 mg/dL (2.28 mmol/L), β -hydroxybutyrate level, 2.1 mg/dL; C-peptide level, 3.6 ng/mL; and serum insulin level, 16.6 μ IU/mL (115.29 pmol/L) (Table). Because of recurrent unprovoked hypoglycemic episodes, a fasting study is not performed. Other laboratory tests at the time of hypoglycemia show normal levels of cortisol, free fatty acids, growth hormone, lactic acid, and pyruvate. In addition, magnetic resonance imaging (MRI) of the abdomen reveals a 10-mm nodule in the head of the pancreas. She is prescribed diazoxide 50 mg 3 times daily and is discharged from the hospital. She tolerates the medication well at home without hypertrichosis or fluid retention, but she continues to have frequent hypoglycemic episodes. In addition, she is noncompliant with home glucose checks, checking only when severely symptomatic. Further testing reveals the diagnosis.

TABLE. Timeline of Events in the Emergency Department

| | INTERVENTION | | | INTERVENTION | | | INTERVENTION | | |
|---|--------------|---|-------------------------|--------------|----|---|-------------------------|---|---|
| Fingerstick glucose, mg/dL | 21 | → | One ampule dextrose 50% | → | 60 | → | One ampule dextrose 50% | → | 53 40 |
| | | | | | | | | | → Intravenous fluids dextrose 5% in 0.45% normal sodium started |
| Serum glucose, mg/dL | | | | | | | | | 41 |
| Insulin, μ U/mL Reference range, 2.6-24.9 μ U/mL | | | | | | | | | 16.6 |
| C-peptide, ng/mL Reference range, 1.1-4.4 ng/mL | | | | | | | | | 3.6 |
| β -hydroxybutyrate, mg/dL Reference range, 0.2-2 mg/dL | | | | | | | | | 2.1 |

DISCUSSION

Given her history of pancreatic head mass and hypoglycemic episodes, insulinoma was strongly suspected. Her previous evaluation showed normal insulin levels, inappropriate in the setting of hypoglycemia. During her second hospitalization, she was intermittently hypoglycemic despite a conservative wean of dextrose-containing fluids, good oral intake, and an increased dose of diazoxide. Calcium levels were normal, reassuring against the presence of parathyroid pathology, which would be concerning for multiple endocrine neoplasia type 1 (MEN1) syndrome. Her physical examination lacked features concerning for tuberous sclerosis or neurofibromatosis. In addition, follicle-stimulating hormone, luteinizing hormone, estradiol, thyrotropin, free thyroxine, prolactin, corticotropin, and insulinlike growth factor-1 levels are appropriate.

Previous MRI showed a discrete lesion in the head of the pancreas (Fig 1). A computed tomographic (CT) scan focusing on the pancreatic area showed an ill-defined nodule in close proximity to the common bile duct and anterior surface of the inferior vena cava. Endoscopic ultrasonography paired with fine-needle aspiration showed a similar lesion corresponding to the location seen on CT. Fine-needle aspiration performed during endoscopy revealed tumor cells consistent with insulinoma. Pediatric surgery was consulted, and an enucleation of the pancreatic tumor was performed. Further histologic examination of tissues obtained revealed a low-grade, well-differentiated neuroendocrine tumor limited to the pancreas, which diffusely stained positive for insulin by immunohistochemistry (Fig 2). After surgery, she was euglycemic, and non-fasting insulin levels decreased to appropriate levels.

The Condition

Insulinoma is a rare neuroendocrine tumor, with an incidence of less than 5 per million people per year. (1) The mean age at diagnosis is 50 years, (2) making this pediatric presentation unique. This tumor causes hyperinsulinism and hypoglycemia, producing a clinical picture of repeated episodes of tremulousness, diaphoresis, confusion, and difficulty with arousability. In less than 10% of cases, the tumor is malignant or associated with MEN1. (2) Moreover, cases of pediatric insulinoma show an association with neurofibromatosis type 1 and tuberous sclerosis, (3) but our patient did not have the skin findings or other clinical manifestations of both diseases.

Congenital hyperinsulinism, a condition affecting β islet cells, also presents with hyperinsulinism and hypoglycemia

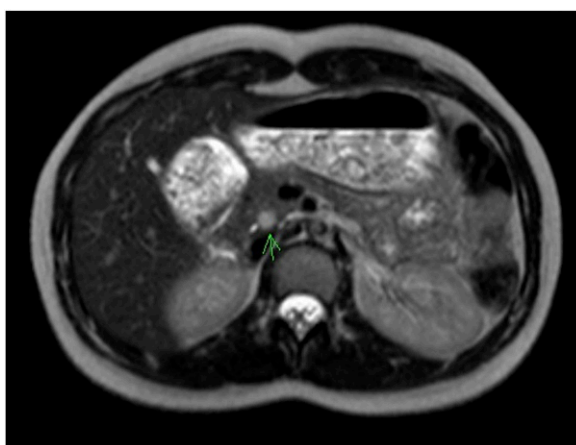


Figure 1. T2-Weighted axial magnetic resonance image of the abdomen showing a lesion (green arrow) at the head of the pancreas.

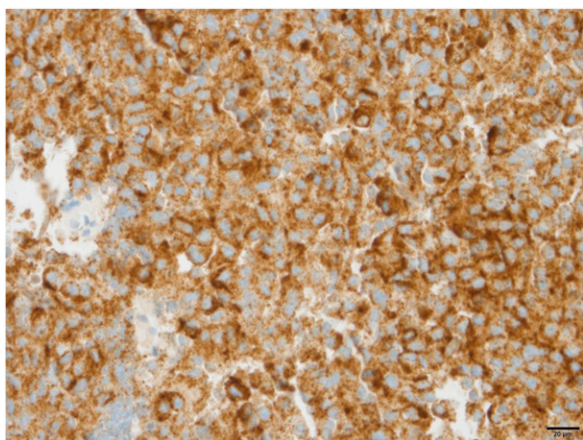


Figure 2. Lesion diffusely positive for insulin (insulin immunohistochemical stain, $\times 40$).

in pediatric patients. However, this condition is primarily seen in patients younger than 18 months. Of the 2 subtypes, the diffuse is twice as common as the focal and represents a more complicated treatment challenge. (2)

Diagnosis

Historical diagnostic criteria for insulinoma, named the Whipple triad, include fasting hypoglycemia, symptoms of hypoglycemia, and resolution of symptoms with glucose administration. (4) Serum study-based diagnostic criteria may require a 72-hour fast with measurement of inappropriately elevated insulin or proinsulin levels and suppression of ketone levels. (5) Iatrogenic or factitious hypoglycemia can be evaluated with C-peptide and sulfonylurea levels.

Localization of the tumor is required to confirm the number and location of the tumor(s) and to guide surgical interventions. Insulinomas are typically singular and benign but may be multiple and scattered throughout the pancreas in cases associated with MEN1. Both CT and MRI are highly sensitive for insulinomas, especially larger ones. Arterial calcium stimulation of insulin release with venous sampling can aid in localization of smaller insulinomas to the appropriate region of the pancreas. (6) Although not widely available, the most useful imaging technique is 18F-DOPA positron emission tomography combined with enhanced CT. (7) Recent studies have also found this technique using gallium DOTA-(Tyr3)-octreotate (Ga-DOTATATE) to be a useful adjunct study when the results of other imaging studies are negative. (8) Endoscopic ultrasonography offers the possibility for fine-needle aspiration and histologic study of the tumor before resection, as was performed

in our patient. Immunohistochemical studies for the presence of chromogranin A, insulin, synaptophysin, and Ki-67 are indicated. (9) Chromogranin A and synaptophysin are specific markers of neuroendocrine cells, and Ki-67 expression and mitotic index are used for grading. Some insulinoma samples may not stain positively for insulin, perhaps due to its rapid release from cells. (8)

Management

Surgical removal provides definitive treatment for insulinoma. The procedure involves enucleation and possibly removal of a portion of the pancreas. Rarely, complete pancreatectomy, and even a Whipple procedure, is performed for insulinoma. (2) It is typically an open procedure rather than laparoscopic. Intraoperative ultrasonography is routinely used to confirm tumor location. Ethanol ablation has been used successfully in some patients deemed prohibitively high risk for surgery. (10)

Medical management for patients who await, refuse, or are poor candidates for surgery is aimed at preventing symptomatic hypoglycemia. Diazoxide decreases insulin secretion but may cause edema and hirsutism. (2) At higher doses, somatostatin analogues such as octreotide inhibit the release of insulin but also of glucagon and growth hormone. (4)

Lessons for the Clinician

- Effects of (recurrent) hypoglycemia, when severe, can result in seizures, loss of consciousness, coma, brain damage, and even death, so early recognition and prompt treatment is imperative and warrants further investigation to determine the underlying cause.
- Insulinoma, seen mostly in adults, can also affect the pediatric population. Once a diagnosis has been established, definitive surgical treatment should be prioritized. Medical management is available for those who are poor surgical candidates or who are not interested in surgical treatment.
- Insulinoma is usually benign and not commonly related to multiple endocrine neoplasia type 1, neurofibromatosis type 1, or tuberous sclerosis syndromes.
- Accurate localization using different noninvasive imaging modalities, or in some cases use of intraoperative ultrasonography, is key to surgery planning and excision of tumor(s).

References for this article are at <http://pedsinreview.aappublications.org/content/39/11/565>.

Case 3: Recurrent Symptom of Sleepiness in an Adolescent Girl
Jocelyn K. Lambuth, Hector F. Lantigua, Monaliza S. Evangelista, Amanda
Tchakarov and Avni Shah
Pediatrics in Review 2018;39;565
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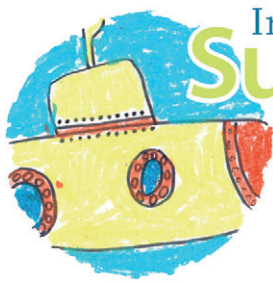
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Index of Suspicion

2 Red Toes in a 17-day-old Boy

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AUTHOR DISCLOSURE Drs Sears, Perez, and Shriner have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy 17-day-old boy is admitted to the hospital due to erythema of bilateral halluces. On the day of admission, he first was taken to an urgent care facility for this issue, where the mother was advised to bring him to the pediatric emergency department for the evaluation of possible herpetic whitlow. His mother first noticed that both of his big toes were becoming progressively “more red than usual” over the past week. He is eating, urinating, and defecating normally. There has been no fever, diarrhea, vomiting, inconsolability, or rash, and he is developing normally. He is not exhibiting signs of experiencing pain. Mom does occasionally get fever blisters. She has not trimmed the toenails in question due to inability to access them.

On presentation he is afebrile and his vital signs are within normal limits. He appears well. Physical examination is significant only for erythematous distal halluces, with the distal nails coursing beneath the inflamed tissue.

A quick bedside search of the medical literature is performed and reveals the diagnosis, obviating antiviral therapy and further laboratory/radiologic evaluation.

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/6/311>.

DISCUSSION

The diagnosis in this case is congenital ingrown toenail of the hallux (CITH) (Figs 1–4), grade 2 variation by the classification system of Honig et al. (1) It is an entity that begins in utero when the distal nail bed of the hallux is short and becomes entrapped in an overabundance of normal soft tissue. The grading system is described as follows: normal—nail plate is growing out over the end of the toe without impedance by tissue; grade 1 variation—the nail plate is curved at its distal end growing up and over the tissue at the distal end of the great toe; and grade 2 variation—the distal end of the nail plate appears to be growing right into the tissue at the distal end of the great toe. (1) The noted erythema occurs as the nail plate grows through the distal tissue, inducing local inflammation with formation of granulation tissue. It has been noted that once the nail plate successfully migrates to its normal length, the redundant superior tissue simply falls off.

There are a limited number of studies available in the literature to guide clinicians in the diagnosis and management of this condition. The prospective study by Honig et al in 1982 (1) has proved to be one of the most influential. In this study, 302 newborns that were admitted to the normal newborn nursery were followed for 1 year. Seventeen percent of these children were found to have a grade 2 variation similar to our patient. By 6 months, all grade 2 variations had spontaneously resolved without intervention, and they had no increased risk of paronychia, suggesting that this finding was a normal variation. (1)

Authors have variously described both inherited patterns and sporadic occurrences, likely due to the capability of different processes of malformation to produce similar findings. The study by Honig et al (1) did not identify an inheritance pattern.

The differential diagnosis should include, as noted appropriately by other clinicians in this case, herpetic whitlow and



Figure 2. Medial view of the left hallux.

paronychia. Other congenital nail malformations can present similarly, such as that described by Chapman et al (2) where the nail growth plate is angularly skewed and overgrowth can occur. The differing inheritance pattern and differing nail plate pathology indicate, however, that these findings are part of a separate pathological process that did lead to predisposition to paronychia as young adults but not as infants.

Management suggestions have similarly varied in the literature. Honig et al (1) showed that conservative management with observation led to complete resolution of the grade 2 CITH by 6 months of age. Others, including Grassbaugh et al, (3) reported persistent cases requiring surgical correction by “fish-mouth incisions” and resections of the “distal tufts of soft tissue in which the nail plates were incarcerated.” All operations were successful without recurrence. The exact type of overgrowth is also likely important given that end-on overgrowth, as in our patient, may behave differently than lateral overgrowth. Regardless, there is strong consensus that the first line of therapy should be



Figure 1. Dorsal view of the left hallux.



Figure 3. Dorsal view of the right hallux.



Figure 4. Medial view of the right hallux.

observation. Some clinicians believe that the erythema warrants antibiotic therapy due to concern of concomitant paronychia, whereas others believe that this is unnecessary.

Outcome

Our patient presented with distinctive bilateral nail findings coincident with erythema that prompted us

to search for alternative causes. A bedside literature search readily revealed the correct diagnosis to be CITH. The plastic surgery department was consulted, and conservative management was recommended. The case was successfully managed without antibiotic therapy, with normalization of bilateral halluces by 6 months of age.

Lessons for the Clinician

- A close examination of the nails for malformation is warranted in any infant presenting with erythematous digits.
- Congenital ingrown toenail of the hallux, a relatively less discussed diagnosis, should be included in the differential diagnosis of infantile erythematous halluces.
- Most commonly, observation with conservative management is successful. There is a potential need for surgical consultation after 6 months, or sooner in consultation with parents, if resolution does not occur spontaneously.

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Case 2: Red Toes in a 17-day-old Boy
William Sears, Cristina Perez and Andrew Shriner
Pediatrics in Review 2018;39;311
DOI: 10.1542/pir.2017-0060

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2 Refusal to Walk in a 2-year-old Girl

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AUTHOR DISCLOSURE Drs Bashir and Aarons have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 2-year-old girl presents with refusal to walk. Her symptoms started 3 weeks ago at child care with fever (104°F [40°C]) and difficulty bearing weight on both lower extremities. A bilateral lower extremity radiograph taken at a local emergency department at that time was unremarkable, but she was found to have acute otitis media and was treated with a course of amoxicillin. After a week the child's limp worsened, causing her to seek treatment at a community clinic, where she was prescribed ibuprofen and heating pads. The progression of symptoms brings her to our hospital. There is no history of trauma or respiratory symptoms. Three months ago she had an episode of bloody diarrhea positive for *Escherichia coli* and *Shigella*. Her immunization record is up-to-date.

On physical examination, she appears comfortable and alert. Her temperature is 98.4°F (36.9°C), heart rate is 100 beats/min, respiratory rate is 24 breaths/min, and blood pressure is 84/60 mm Hg. Examination of her lower extremities is limited due to poor cooperation. It is difficult to determine whether the patient has leg tenderness because lower extremity motion elicits pain. There seems to be full range of motion bilaterally of the hips and knees. Deep tendon reflexes cannot be elicited in the lower extremities at both knees and ankles. There seems to be a slight increase in muscle tone of the lower extremities, but this can be due to an examination error. There is limited dorsiflexion of the right foot. There is no swelling or erythema at any of the joints in the lower extremities. The remainder of the examination findings are normal.

Her complete blood cell count, comprehensive metabolic panel, creatine kinase level, antinuclear antibodies, and C-reactive protein (CRP) level are all within their respective normal ranges. The erythrocyte sedimentation rate (ESR) is slightly elevated at 25 mm/hour. Lower extremity radiographic and bone scan findings are negative. Additional evaluation leads to the diagnosis.

The Case Discussion and Suggested Readings appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/1/38>.

DISCUSSION

Magnetic resonance imaging (MRI) of the spine demonstrated inflammatory demyelinating polyneuropathy, and a cerebrospinal fluid (CSF) analysis showed normal white and red blood cell counts and a high protein concentration of 0.1 g/dL (1.0 g/L), thus establishing the diagnosis of Guillain-Barré syndrome (GBS). The patient was treated with intravenous immunoglobulin (IVIg) and was then transferred to a rehabilitation center for continued care.

The Condition

Guillain-Barré syndrome is a postinfectious polyneuropathy involving mainly motor nerves, but it can also affect sensory and autonomic nerves. It is the most common cause of acute flaccid paralysis in the pediatric population. A preceding diarrheal infection with *Campylobacter jejuni* is most commonly associated with GBS. However, infections with Epstein-Barr virus, cytomegalovirus, and mycoplasma pneumoniae have also been associated with the development of GBS.

The classic presentation of GBS is an acute ascending flaccid paralysis, but many clinical variants exist. Weakness is usually symmetrical and begins in the lower extremities progressing upward toward the trunk. There is often associated paresthesia and pain contributing to inability to walk. Classically, deep tendon reflexes are lost, although they may be preserved until late in the disease. Involvement of the diaphragm can lead to respiratory compromise, and these patients may need mechanical ventilation. Dysphagia and facial weakness can be subtle signs of impending respiratory failure. Some patients experience autonomic instability, leading to hypotension or hypertension, cardiac dysrhythmias, bladder dysfunction or abnormal sweating. Thus, these patients require close cardiorespiratory monitoring. The severity of illness greatly varies among individuals, with some progressing over hours and others over weeks.

Differential Diagnosis

The differential diagnosis of a limping child is broad. One of the most common causes of limping in young children is toxic synovitis. It is usually preceded by an upper respiratory tract infection and responds well to nonsteroidal anti-inflammatory drugs and heating pads. Another diagnosis we considered was juvenile idiopathic arthritis, but lack of a rash, joint swelling, erythema, or warmth makes it less likely.

Infectious etiologies such as septic arthritis, postinfectious myositis, and osteomyelitis were also considered. These would present with fever, and laboratory studies would show elevated

CRP levels and leukocytosis on complete blood cell count. The bone scan results would be positive, showing focally increased uptake and focal hyperemia. Diskitis is another condition that has an acute onset in children and that can present with refusal to walk and a normal white blood cell count; however, the CRP level and ESR would be significantly elevated.

Ultimately, concern for spinal cord lesions and demyelinating diseases prompted a spinal MRI. Her clinical history, physical examination, MRI, and then CSF findings support the diagnosis of GBS.

The Diagnosis

The diagnosis is established by a combination of clinical presentation (preceding gastrointestinal or respiratory tract infection, progressive weakness, pain, paresthesia, and areflexia) combined with CSF analysis, MRI of the spinal cord, and, occasionally, electrodiagnostic studies or antibody studies. Analysis of CSF usually demonstrates elevated CSF protein levels (>0.045 g/dL [0.45 g/L]), with a normal CSF leukocyte count. This is known as albuminocytologic dissociation. The CSF protein level may not be elevated early in the course of the disease.

Management

Treatment of GBS consists of supportive care and administration of IVIg or plasma exchange. The use of IVIg is preferred in the pediatric population because plasma exchange is an invasive and time-consuming procedure. Regardless, both treatments yield excellent recovery in the pediatric population compared with adults. The mortality rate is 3% to 4%, with a recurrence rate of 2% to 5%.

Lessons for the Clinician

- Guillain-Barré syndrome should be considered in the differential diagnosis of a child with a limp.
- Classically, deep tendon reflexes are lost, although they may be preserved until late in the disease.
- Dysphagia and facial weakness can be subtle signs of impending respiratory failure.
- Making an accurate diagnosis in a timely manner can help avoid unwanted consequences of Guillain-Barré syndrome, such as diaphragm paralysis requiring mechanical ventilation and cardiac arrhythmias.

Suggested Readings

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6 Seizures and Low Cerebrospinal Fluid Glucose in a 4-day-old Boy

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AUTHOR DISCLOSURE Drs Belal and Chandra have disclosed no financial relationships relevant to this article. Dr Day-Salvatore has disclosed that she has research grant funding for registries and clinical trials from Sanofi Genzyme related to lysosomal storage diseases. She also serves as a lysosomal storage disease expert for Sanofi Genzyme and receives travel reimbursement and honoraria from the company. Dr Belal's current affiliation is Mount Washington Pediatric Hospital, Baltimore, MD. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 38-week, appropriate-for-gestational age boy born to a 31-year-old primigravida mother and a 36-year-old father by emergency cesarean delivery due to failure-to-progress and fetal distress 26 hours after spontaneous rupture of membranes with clear amniotic fluid is admitted electively to the NICU for possible severe bacterial infection as the mother developed an intrapartum fever. Pregnancy was normal. Apgar scores were 9 and 9 at 1 and 5 minutes, respectively. There were no reported exposures to tobacco, alcohol, or drugs. The newborn is asymptomatic on admission. His birthweight is 3,070 g (40th percentile), length is 51 cm (80th percentile), and head circumference is 32.5 cm (20th percentile). His temperature is 98.6°F (37°C), heart rate is 130 beats/min, respirations are 40 breaths/min, oxygen saturation is 99% on room air, and blood pressure is 69/34 mm Hg. Physical examination is notable only for a small right preauricular tag. He shows no dysmorphic features; anterior fontanelle is flat and patent; red reflex is present bilaterally; chest is clear to auscultation; heart sounds are normal, with no clicks, murmurs, or gallops; abdomen is lax, with no palpable organs or masses; both testicles are descended in the scrotum; and Tanner stage is 1. No rashes, lesions, or birthmarks are noted on the skin, and primitive reflexes are present.

The child receives ampicillin and gentamicin for 48 hours. Blood culture results are negative. On day 4, the newborn starts to have feeding intolerance that progresses to episodes of apnea, desaturations, and eye rolling, with “arm bicycling”-like movements. A repeated evaluation for possible sepsis is initiated. Antibiotics are started again, along with acyclovir. Results of brain computed tomographic scanning and magnetic resonance imaging are normal. Cerebrospinal fluid (CSF) and blood cultures and CSF herpes simplex virus polymerase chain reaction return negative. Complete blood cell count, C-reactive protein level, serum ammonia level, bicarbonate level, electrolyte levels, and results of state newborn screening are all normal. The CSF analysis shows a white blood cell count of 3/μL ($<0.001 \times 10^9/L$), no red blood cells, a protein level of 0.1 g/dL (1 g/L), and a glucose level of 34 mg/dL (1.9 mmol/L), along with a serum glucose level of 87 mg/dL (4.8 mmol/L). A video electroencephalogram captures multiple seizure episodes. Leviteracetam and phenytoin treatment is initiated. Lumbar puncture

repeated after 4 hours of fasting shows a CSF glucose level of 30 mg/dL (1.7 mmol/L) along with a serum glucose level of 95 mg/dL (5.3 mmol/L) at the time of the spinal tap in the absence of red or white blood cells. The newborn continues to have seizures despite taking antiepileptics. Further family history obtained is remarkable for history of seizures in the patient's mother during childhood and a seizure disorder in the maternal aunt and her son. Due to low CSF

glucose level–associated seizures with a concomitant normal serum glucose level, a specific genetic disorder is suspected. Additional genetic testing confirms the diagnosis. A special diet results in termination of the seizures.

The Case Discussion and Suggested Readings appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/5/265>

DISCUSSION

SLC2A1 gene sequencing revealed heterozygosity for a missense mutation resulting in substitution of glycine for arginine at amino acid position 153, which the laboratory classified as a variant of unknown significance. However, 2 other variants altering this specific amino acid have been reported in 3 patients with GLUT1 transporter deficiency syndrome (GLUT1-DS), also known as De Vivo disease. The CSF metabolome also showed very low levels of glucose, fructose, and mannose and very high levels of glutamine and inosine suggestive of GLUT1-DS.

The Condition

GLUT1-DS is a rare autosomal dominant disorder due to a mutation in or deletion of the *SLC2A1* gene found at chromosomal location 1p34.2, which encodes for GLUT1 transporter that is responsible for basal glucose across the blood-brain barrier. Symptoms result from neuroglycopenia due to inability of glucose to be transported from the blood to the brain. The classic presentation includes early-onset seizures and neurodevelopmental delays in infancy or childhood. Some patients present with a nonepileptic form with paroxysmal movement disorders in childhood or even later in adulthood with intermittent ataxia, choreoathetosis, dystonia, or alternating hemiplegia. Rarely, the condition is inherited in an autosomal recessive manner. Hypoglycorrhachia (low CSF glucose level) with a normal serum glucose level (measured simultaneously) is the accepted standard for making this diagnosis. Ideally, CSF and serum glucose levels should be measured after 4 hours of fasting. The level of CSF glucose is typically less than 60 mg/dL (<3.3 mmol/L) (in most cases it is <40 mg/dL [<2.2 mmol/L]). The CSF/blood glucose ratio is usually less than 0.4. Other abnormal biochemical tests include low or low normal CSF lactate. An uptake assay to measure glucose transport across the cell membrane can be performed by assessing erythrocyte 3-O-methyl-D-glucose uptake. It is expected to be abnormally low, but this test may not be readily available. Molecular genetic testing can confirm the diagnosis by detecting a pathogenic variant in the *SLC2A1* gene by sequence analysis or deletion/duplication analysis. Metabolome testing is a newly emerging study that can assess hundreds of small metabolites with a single screening test looking at perturbations in biochemical pathways. It can aid in the diagnosis of many inborn errors of metabolism. In GLUT1-DS, CSF metabolome analysis is expected to show low levels of glucose, fructose, and mannose along with high levels of glutamine and inosine.

Treatment

Antiepileptic drugs are ineffective in treating GLUT1-DS. The treatment of choice is the ketogenic diet because

ketones cross the blood-brain barrier through MCT1 transporter not GLUT1 transporter. Ketones provide an alternative source of energy to brain cells. Studies have shown that early identification of this disease and early management with the ketogenic diet are associated with better neurodevelopmental outcomes. Our patient became seizure-free and his electroencephalogram normalized after the ketogenic diet was initiated. He was not taking any anti-epileptic drugs on discharge. At the follow-up visit at 4 months of age he showed age-appropriate growth and development and remained seizure-free solely on the ketogenic diet. It is possible that our patient's family history of seizures in the mother, maternal aunt, and her son is due to GLUT1-DS, but the family refused further genetic testing.

Lessons for the Clinician

- Subtle seizures should be included in the differential diagnosis of apnea in newborns.
- Clinicians should be aware that although low cerebrospinal fluid glucose (hypoglycorrhachia) can be suggestive of an infectious etiology, it is not always the case. Other causes of hypoglycorrhachia, such as GLUT1 transporter deficiency syndrome (GLUT1-DS), should be considered, particularly if the patient has a concomitant seizure or movement disorder.
- Clinicians should be aware of the broad spectrum of presentation of GLUT1-DS from infancy into adulthood and the importance of early recognition of this disorder. The ketogenic diet should be started promptly on suspicion of this disorder because it is the only proven effective treatment to improve neurodevelopmental outcomes.

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3 Skull Depression in a 9-month-old Girl

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AUTHOR DISCLOSURE Drs Galvis, Shoo, and Shedlock have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 9-month-old unvaccinated African American girl presents to the emergency department for the evaluation of an abnormal head “bump.” The mother reports that 5 days before presentation the patient rolled over off a bed and fell 3 feet to the ground. After the fall the girl exhibited no behavioral changes, apparent pain, or emesis. Since the incident, the mother reports that the patient has been doing well, although she became concerned 2 days ago when she noticed a depression on her daughter’s head while bathing her.

The infant was born full term but small for gestational age. The mother reports no complications with the birth but that a radiograph was obtained in the nursery showing bilateral “bowed legs.” However, the patient was lost to follow-up after nursery discharge with no establishment of a primary care physician.

On examination in the emergency department, her vital signs are as follows: temperature, 98°F (36.7°C); heart rate, 156 beats/min; respiratory rate, 34 breaths/min; and oxygen saturation, 98% on room air. The patient’s weight and height are both below the third percentile. The patient is interactive and playful. There is a small depression 1.6 in (4 cm) in diameter on the left parietal region of her head, with no crepitus or tenderness to palpation. The remaining physical examination findings are normal except for yellowish translucent teeth.

Laboratory studies are obtained and show a complete blood cell count and complete metabolic profile within normal limits. A head computed tomographic scan without contrast illustrates a 13-mm depressed comminuted left parietal skull fracture with possible small underlying subarachnoid hemorrhage (Fig 1). Additional imaging and laboratory evaluation lead to the diagnosis.

DISCUSSION

A skeletal survey obtained in the emergency department showed multiple fractures, including a “ping-pong” type of fracture of the posterior left parietal bone (Fig 2), a healed deformity of the proximal left femoral shaft (Fig 3), slight loss of height of the midthoracic vertebral bodies, and diffuse bone undermineralization. Trauma surgery was consulted, and Child and Protective Services was called for suspicion of nonaccidental trauma (NAT). The patient was admitted to the PICU for monitoring, where ophthalmologic examination findings were negative for retinal hemorrhages.

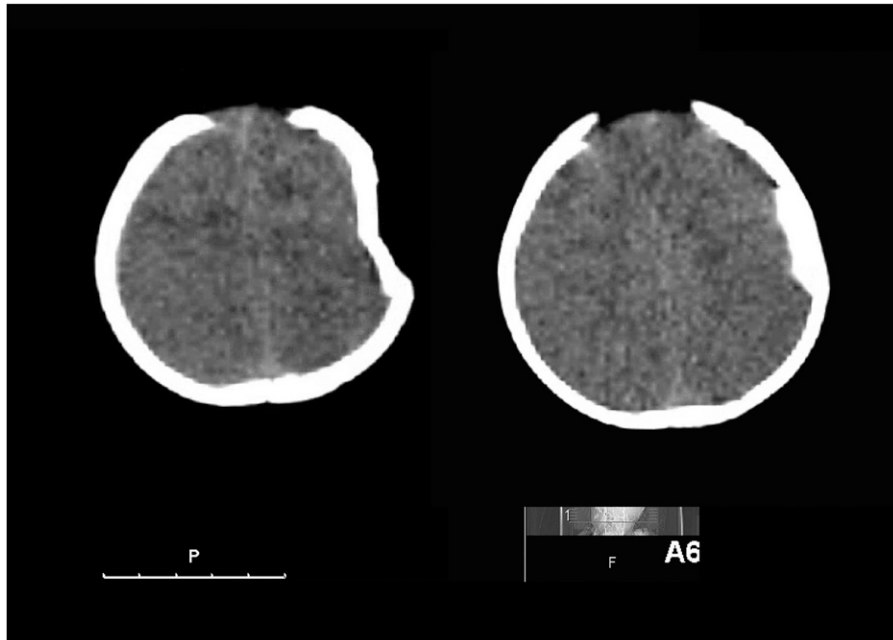


Figure 1. Computed tomographic scan illustrates a 13-mm depressed comminuted left parietal skull fracture with possible small underlying subarachnoid hemorrhage.

The mother, on further questioning, reported that the father of the child has a history of fractures due to minor trauma. An extensive review of the patient's newborn records showed that prenatal ultrasonography was concerning for a possible congenital bone disorder. An endocrinologist and a geneticist were consulted; both recommended additional laboratory tests for further evaluation. Growth hormone markers insulin-like growth factor-1 and insulin-like growth factor binding protein 3, thyroid

studies, a celiac panel, erythrocyte sedimentation rate, complete metabolic profile, prealbumin level, and genetic testing for osteogenesis imperfecta (OI) targeting the genes *COL1A1* and *COL1A2* were ordered. During the hospital stay, all the laboratory test results were normal, with the genetic study results pending. Orthopedic surgery and neurosurgery cleared the patient for discharge without the need for further intervention. She was discharged to her maternal grandmother, with Child and Protective Services closely following her while the genetic evaluation was pending. A month after discharge the genetic results confirmed the diagnosis of OI with a point nucleotide mutation of guanine to thymine in exon 17 of the *COL1A2* gene (converting glycine to cysteine). This mutation has not been previously reported, so disease severity cannot be predicted.

Differential Diagnosis

The differential diagnosis for OI includes NAT and a variety of skeletal conditions associated with bone deformities, such as hypophosphatasia and rickets. The appearance of multiple fractures in various stages of healing can make distinguishing NAT from OI very difficult. Information that may lead the clinician toward a diagnosis of OI includes a positive family history, poor growth, born small for gestational age, hearing loss, dentinogenesis imperfecta, long bone deformity, and/or blue sclera. (1)(2)

Although the birth history made a congenital bone disease concerning, the delayed emergency department



Figure 2. Skeletal survey shows a "ping-pong" type of fracture of the posterior left parietal bone.

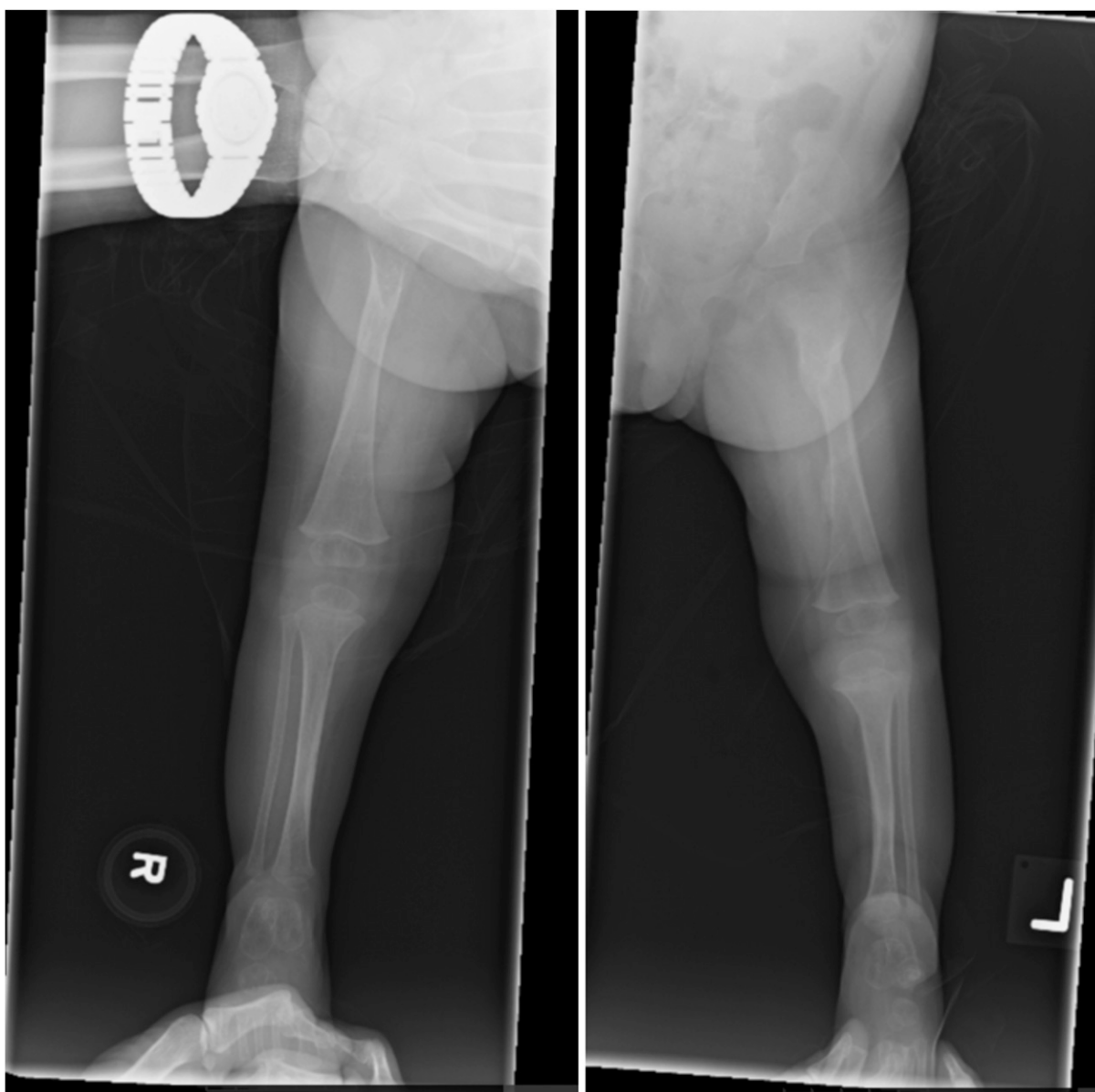


Figure 3. Skeletal survey shows a healed deformity of the proximal left femoral shaft.

presentation, lack of an outpatient pediatrician, and unvaccinated status raised the suspicion for NAT. It is important to note that some studies estimate that a child is 24 times more likely to have a fracture caused by NAT than from OI. (3) Hypophosphatasia, unlike OI, causes decreased serum alkaline phosphatase levels, but this patient had normal serum levels. Rickets can cause growth retardation, abnormal tooth formation, defective bone mineralization, and elevated alkaline phosphatase similar to OI. However, rickets has specific radiographic findings, including widening of the epiphyseal plates, metaphyseal cupping, looser zones, and rachitic rosary. In this case, a clinical diagnosis of OI was made when considering the history, imaging, laboratory, and

clinical findings (especially the yellow translucent teeth), which was later confirmed with genetic testing.

The Condition

Osteogenesis imperfecta is a rare disorder that occurs at a rate of 1 per 20,000 live births and is considered an orphan disease. It has multiple forms of inheritance but is most frequently autosomal dominant. It is caused by a mutation in genes encoding alpha 1 and alpha 2 chains of type 1 collagen or by a mutation in proteins involving posttranslational modification of type 1 collagen fibers. (2)(4) The original classification by Sillance in 1979 proposed 4 OI types that were based on clinical and radiologic findings only. In 1981,

Barsh and Byers (5) were the first to find reduced secretion of structurally normal type I procollagen in a patient with OI. By the end of that decade it was understood that nonsense and missense mutations of collagen genes (*COL1A1/COL1A2*) give rise to type I and types II to IV OI, respectively. As of 2015, with recent advancements in molecular technologies, the classification has been expanded to include up to 17 types of OI and the rare disorders Bruck syndrome 1 and 2, which are a combination of OI with contractures. (2)(6)

Clinical manifestations of OI can include excess or atypical fractures, short stature, scoliosis, basilar skull deformities that can cause neurologic symptoms, blue sclerae, progressive hearing loss, dentinogenesis imperfecta, increased laxity of the ligaments and skin, wormian bones, and easy bruising. Many of these patients eventually develop significant morbidity from respiratory insufficiency.

Diagnosis

The clinical diagnosis of OI as proposed by the 2015 Nosology and Classification of Genetic Skeletal Disorders can be fairly straightforward when there is a positive family history, typical physical features, and radiologic findings as previously described. However, in milder cases, where few clinical symptoms are observed and/or the family history is unknown, making a definitive diagnosis is more difficult. The current available molecular diagnostic test of OI uses next-generation gene sequencing to target gene panels and, therefore, is more cost-efficient with a faster turnaround time than traditional Sanger sequencing. (7)

Management

Current treatment for OI depends on the severity of disease and starts with establishing a medical home. Current primary care recommendations for all children with OI include routine and frequent screening for hearing, vision, and scoliosis; providing yearly influenza vaccination and the 23-valent polysaccharide pneumococcal vaccines in addition to routine immunizations; and coordinating referrals to subspecialists (genetics, endocrinology, pulmonology, and orthopedics), physical therapy, and occupational therapy to assist in providing comprehensive physiotherapy. The primary goal of the general pediatrician is to work closely with a multidisciplinary team to manage this complex condition and prevent its complications. (8)

Children with mild type I OI who have normal physical activity can manage any acute fractures with orthopedic surgery and rehabilitation services. Children with moderate-to-severe OI who experience long bone deformities, scoliosis, and reduced mobility may benefit from more aggressive interventions, including bone antiresorptive

therapy with the use of intravenous bisphosphonates. (6) Some studies have shown that these medications increase bone mass density, decrease fractures, and improve the functional status of patients overall. However, due to expense, adverse effects (hypocalcemia, fever, vomiting), and a lack of significantly powered clinical trials, the bisphosphonates are usually reserved for moderate-to-severe disease at the discretion of the bone health team. (2) In addition to medication, patients can benefit from surgical correction of limb bowing over time if necessary.

Our Patient

Before discharge from the hospital, a medical home was identified for the patient and her care team was notified of her diagnosis, hospital course, and follow-up recommendations. On her first visit with her primary care physician, a rapid immunization catch-up was initiated, and the patient was referred to the pediatric endocrinology, orthopedic surgery, genetic counseling, and early intervention services for physical therapy and occupational therapy to help maximize bone health while formulating a plan for safe physical activity and ambulation as the patient progresses in her motor development. Unfortunately, she has since experienced another femur fracture before being fully integrated into the care of a multisubspecialty team, which has delayed the initiation of bisphosphonate therapy and comprehensive physiotherapy.

Lessons for the Clinician

- Not all skull fractures accompanied by other fractures in different stages of healing are child abuse.
- Clinicians should consider congenital or acquired bone disease such as osteogenesis imperfecta, rickets, or hypophosphatasia in the differential diagnosis of non-accidental trauma, especially with a personal or family history of frequent fractures, abnormal sclerae, or atypical teeth.
- For concerning findings in the newborn nursery, subspecialist consultation before discharge to establish a diagnosis and/or careful follow-up of abnormal studies (including contacting the chosen primary care provider) are crucial to prevent delay in care and to limit complications.
- Osteogenesis imperfecta is a complex genetic condition that causes excessive fractures and requires a well-coordinated medical home using the hallmark therapies of bisphosphonates and physiotherapy to optimize growth, development, and bone health.

References for this article are at <http://pedsinreview.aappublications.org/content/39/7/366>.

Case 3: Skull Depression in a 9-month-old Girl
Alvaro Galvis, Anthony Shoo and Aaron R. Shedlock
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2 Sore Throat and Dysphagia in a 6-year-old Boy

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AUTHOR DISCLOSURE Dr Belfer has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy, fully vaccinated 6-year-old boy presents to the emergency department with sore throat and difficulty swallowing starting the previous evening. That morning the boy had complained of difficulty swallowing when eating breakfast and was noted to have some drooling. He was given acetaminophen before presenting to the emergency department. The boy has a history of enlarged tonsils, but no other pertinent medical history.

At presentation, he is febrile (102.7°F [39.3°C]), with a heart rate of 151 beats/min, respiratory rate of 20 breaths/min, blood pressure of 109/63 mm Hg, and oxygen saturation of 99% on room air. On physical examination the boy is noted to be ill appearing, with enlarged and erythematous tonsils. Neck examination is significant for tenderness on the lateral aspects bilaterally, with lymphadenopathy of ~2 cm noted on the left and right sides of the neck. There is no stridor or voice change, and the boy has clear breath sounds bilaterally on auscultation. His neck is observed to be supple, with no restriction in range of movement.

Laboratory studies reveal a white blood cell count of 34,000/mL, with 94% neutrophils on the differential cell count. A metabolic panel shows a bicarbonate level of 18 mEq/L (18 mmol/L) but is otherwise normal. Uric acid and lactate dehydrogenase levels are normal. Results of a respiratory viral panel, rapid strep test, and infectious mononucleosis screen are negative.

Imaging revealed the diagnosis.

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/5/260>.

DISCUSSION

Lateral neck radiography was performed and revealed an enlarged epiglottis, concerning for epiglottitis. The patient was given ceftriaxone and dexamethasone, and airway management was immediately instituted. The patient was observed to be very comfortable and in no acute respiratory distress, so a bedside fiberoptic endoscopy was performed by ear, nose, and throat (ENT) specialists. Airway visualization revealed erythema and mild edema of the epiglottis, aryepiglottic folds, and arytenoid cartilages. The airway was observed to be widely patent. The findings confirmed a diagnosis of epiglottitis. The boy was admitted to the hospital and observed on continuous pulse oximetry on the general medicine inpatient floor. Although most children with epiglottitis are admitted to the ICU, the child was deemed to be stable enough from a respiratory standpoint for general medicine floor admission. Ceftriaxone and dexamethasone use were continued. The boy remained stable, with no respiratory distress, and tolerated a normal diet with resolution of his dysphagia. His blood culture grew *Haemophilus influenzae* serotype A at 19 hours of incubation. Follow-up blood cultures the following 2 days showed no growth. The boy was discharged after 2 days and was prescribed cefdinir to complete a total of 10 days of antibiotic drug therapy.

The Condition

Although the incidence of epiglottitis has greatly decreased since the advent of the *H influenzae* type b vaccine, it is a condition that can be quickly fatal when not included on a differential diagnosis. Anatomically, the epiglottis and the bordering arytenoid cartilages create the opening of the larynx. In epiglottitis, a cellulitis of these structures causes inflammation and edema, with the resulting enlargement of the epiglottis creating a risk for obstruction of the airway.

Children with epiglottitis often appear toxic, with rapidly progressive symptoms that can include sore throat, dysphagia, and high fevers. Ultimately, respiratory failure due to obstruction of the airway is responsible for mortality from the condition. Although respiratory distress can be an early or late symptom, children with a partially obstructed airway exhibit the classic “tripod” position: leaning forward while supporting themselves with their arms. Drooling and voice changes can be seen in epiglottitis as well.

Clinically, providers must have a low threshold of suspicion for the diagnosis as a result of the potentially quick progression of disease. Protecting the airway should be the clinician’s top priority, and, therefore, diagnostic evaluation must be weighed against the risk of delaying treatment.

Although laryngoscopy can ultimately confirm the diagnosis, it should be performed only if the patient is clinically stable. If performed, an environment in which the airway can be quickly secured (via intubation or tracheostomy), such as an operating room or an intensive care setting, is strongly recommended. Similarly, imaging should be considered only when the clinical presentation is ambiguous and should be performed only in stable patients. If imaging is performed, the patient should preferably be accompanied by a physician skilled in airway management (ie, an anesthesiologist, intensivist, ENT specialist, or emergency physician) and should be given priority to have the imaging performed in a timely manner. Lateral radiographs show the classic “thumb sign” of the enlarged and edematous epiglottitis. (1)

The creation of the *H influenzae* type b vaccine in the mid-1980s has greatly affected the epidemiology of the resulting diseases, including epiglottitis. Most *H influenzae*-caused infections were seen in children younger than 2 years, with more than 90% of cases seen in children younger than 5 years. In this age group, the annual incidence was estimated to be up to 129 cases per 100,000 children. The incidence has significantly decreased since the vaccine was created, with invasive *H influenzae*-caused disease in the United States currently causing only up to 1 case per 100,000 children younger than 5 years. (2)

With the addition of the *H influenzae* type b vaccine to the standard immunization schedule, the mean age of epiglottitis saw an increase. One study from Boston found a mean age increase of almost 6 years, from 5.8 to 11.6 years old. (3) Similarly, a British study observed a decrease in epiglottitis cases in the population younger than 15 years, with a resulting increase in an older population. (4)

Other causes of upper airway obstruction must be included in a differential diagnosis with epiglottitis. Peritonsillar and retropharyngeal abscesses were considered by the clinicians in this case and can present similarly to epiglottitis, with fevers, drooling, and restricted neck movement. A lateral neck radiograph, performed to diagnose the patient described herein, can be used in the diagnostic evaluation of these conditions. Foreign bodies and congenital anomalies of the upper airway can cause blockage of the airway, but both are usually seen in afebrile children. Although anatomically similar to epiglottitis, an enlarged epiglottis can be caused by trauma, thermal injury, and even radiation to the neck.

The boy in this case came into the emergency department with an atypical, yet much less quickly progressive, presentation of epiglottitis. Although clinically stable, the evolving neck pain with continued fevers suggested to the medical team the possibility of a more serious illness.

Fortunately, he was initiated on antibiotic drug therapy soon enough to prevent a potentially fatal progression of the infection. High suspicion with a low threshold to treat remained true in this case as important clinical pearls in diagnosing and treating epiglottitis.

Lessons for the Clinician

- Epiglottitis must be considered in the differential diagnosis for a patient with sore throat and dysphagia because it can be quickly fatal if untreated.
- The condition should be considered regardless of a patient's vaccination status.
- The age at presentation of epiglottitis has increased since the advent of the *Haemophilus influenza* type b vaccine.
- Most patients with epiglottitis should be cared for in an intensive care setting owing to fear of impending respiratory failure.

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Case 2: Sore Throat and Dysphagia in a 6-year-old Boy

Joshua A. Belfer

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4

Stroke after Minor Trauma in an Otherwise Healthy 18-month-old Boy

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AUTHOR DISCLOSURE Drs Cecchini, Iqbal, and Murnick have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy 18-month-old boy presents to the emergency department (ED) after a fall. His parents reported that the father was carrying the child down the stairs when he slipped 1 step from the bottom; the child fell out of his arms and landed on his chest on the hardwood floor. The child did not lose consciousness and he cried immediately, but several minutes later his mother noticed that he seemed “dazed.” Emergency medical services was called, and the child was alert and awake on their arrival.

The child arrived at the ED 3.5 hours after the fall given the family’s remote location. During his initial examination he was sitting in his mother’s arms with his head held midline and was moving all 4 extremities. The remainder of his examination findings are normal. His mother is very worried that “something” is wrong. He is stratified as intermediate risk for traumatic brain injury, and the decision is made to observe him in the ED.

After a trial of oral intake, he stood up to walk, at which point he is noted to be slightly antalgic. Shortly after that his mother notices right-sided facial droop when he smiles and that his head is tilted to the left. The physician notes decreased movement of the right arm and leg, with only a weak grip in his right hand. A Miami J collar is placed, and head computed tomographic (CT) scans and C-spine radiographs are ordered. The head CT scan reveals the diagnosis. The child is hospitalized in the ICU.

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/6/313>.

DISCUSSION

Differential Diagnosis

Differential diagnosis included intracranial hemorrhage, arterial ischemic stroke, acute arterial dissection, and non-accidental trauma.

After the change in neurologic status, diagnostic studies were performed; C-spine radiographs were negative, and an electrocardiogram showed normal sinus rhythm. A non-contrast CT scan of the head revealed a small chronic infarct of the left caudate head and scattered mineralization in both lateral putamina. It was suggested that the imaging findings and clinical history were most consistent with lenticulostriate mineralizing angiopathy with infarct after minor trauma. The visualized chronic infarct likely represented a previous subclinical stroke, and the presenting symptoms raised suspicion for a new acute basal ganglia infarct not yet visible by CT scanning. Acute infarct was confirmed by magnetic resonance imaging.

The patient underwent a full thrombophilia evaluation because there was a family history of stroke in an uncle at a young age. He was started on aspirin 80 mg by mouth in the ED.

The Condition

Basal ganglia stroke after minor trauma associated with mineralizing angiopathy is an uncommon phenomenon in children, but it is a unique clinicoradiologic entity. (1) The particular findings have been described by previous authors in several case studies and brief series. This specific kind of infarct after minor trauma accounts for less than 2% of all childhood ischemic stroke. (2) The classic age range is described as younger than 18 months but can extend to as old as 26 months. (1) The condition also does not seem to demonstrate cultural or ethnic predisposition. (1) It does, however, seem to have an elevated incidence rate in boys. (1)(3)

Pathophysiology

The pathophysiology is largely unknown, with many proposed theories. Yang et al (3) suggest that the angle between the main middle cerebral artery and the lenticulostriate arteries, which supply the basal ganglia and internal capsule, is more acute in infancy and early childhood and, therefore, more prone to ischemia. (3)

Other authors have suggested that central nervous system cytomegalovirus infection is a risk factor for stroke in the setting of basal ganglia calcification. (3) It is unclear whether CMV infection can itself cause basal ganglia mineralization. (1)

Diagnosis

History and physical examination typically include details of a minor trauma or fall. Hemiparesis and facial paresis occur within 72 hours after the initial insult. (1)(2)(3)(4) Some cases described also report associated convulsion. (4) Typically, there is no evidence of hypercoagulability or an underlying thrombophilic condition. (1) This mineralizing angiopathy is typically visualized on CT scans without contrast, (1) making this modality necessary for diagnosis. The Figure highlights these findings.

Lingappa et al (1) also showed that magnetic resonance imaging studies do not always identify the characteristic mineralization. Furthermore, standard CT scanning does not always reveal the true extent of the vascular mineralization. Therefore, one should consider thin-section spiral CT scans with multiplanar reconstructions, (1) especially if clinical suspicion remains high and other imaging studies are unrevealing.

Management and Prognosis

Conservative treatment is typically the most effective management of choice for basal ganglia stroke in the pediatric population. A review of the literature shows that existing consensus statements do not recommend anticoagulation for children with microvascular disease. Patients are provided with close monitoring and physical therapy. (1)(2)

It has been demonstrated that short- and long-term neurodevelopmental outcomes are good. Although some children demonstrate minor weakness or deficits in their gross motor skills, these tend to improve over time. (1) Most often, hemiplegia typically disappears within 24 hours of presentation. Dharker et al (5) showed that all but 1 of 23

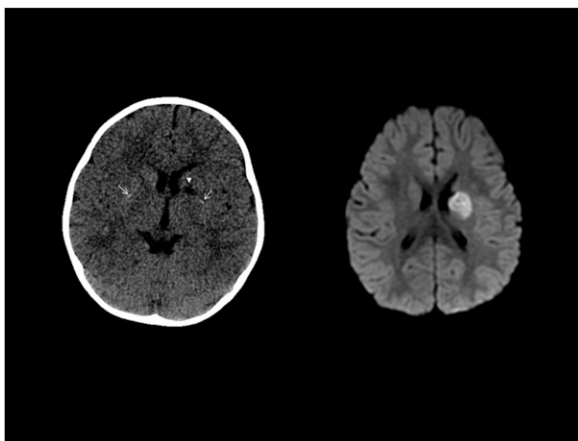


Figure. Left, Axial noncontrast computed tomographic scan demonstrating small linear calcifications in both putamina (arrows) and small chronic infarct involving the left caudate head and internal capsule (arrowhead). Right, Diffusion-weighted magnetic resonance image from the same day demonstrating a larger acute left basal ganglia infarct.

children who developed immediate unilateral weakness after minor head injury recovered completely within 4 months. Although most strokes in this condition are solitary events, a substantial minority of patients experience recurrent events (23% in the largest published series). With recurrent stroke, outcomes are worsened and may include continued hemiparesis and speech delay with fine motor difficulties. (6)

Lessons for the Clinician

- Ischemic stroke is a rare complication of minor head trauma in pediatrics.
- Consider mineralizing angiopathy in a child presenting with minor head trauma and signs of stroke, specifically hemiparesis or facial paresis shortly after the incident.
- Children with mineralizing angiopathy are not typically found to have laboratory findings supportive of an underlying thrombophilic state.
- In the acute period, a combination of noncontrast head computed tomographic scanning (to demonstrate mineralization) and magnetic resonance imaging (to demonstrate acute infarct) is often necessary for diagnosis.
- Conservative treatment and close monitoring generally result in good outcomes for children with mineralizing angiopathy and subsequent basal ganglia stroke after minor trauma.

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5 Ulcerated, Painful Genital and Perianal Rash in a 1-year-old Girl

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AUTHOR DISCLOSURE Drs Chagalamarri and Das have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 1-year-old previously healthy white girl presents to the emergency department with worsening genital and perianal rash. The rash started on her perineum 5 days before presentation and spread quickly to her pudental cleft. Her mother applied an over-the-counter diaper rash ointment with no relief. The toddler is playful but becomes fussy during diaper changes. She had a runny nose and 2 episodes of watery diarrhea in the past week. She has had no vomiting; a decrease in urine output; no oral, ocular, or nasal mucosal involvement; and no vaginal discharge. The older sibling had a red painful blister under her nose 2 weeks ago. The infant has a normal birth history, and her medical history is significant for atopic dermatitis. She has worn the same brand of diapers since her birth. Both her mother and sister help change her diapers at home.

Physical examination reveals a nontoxic-appearing infant with a temperature of 101°F (38.3°C). Other vital signs are within normal parameters. She has diffusely dry skin. Examination of the diaper area reveals multiple punched out

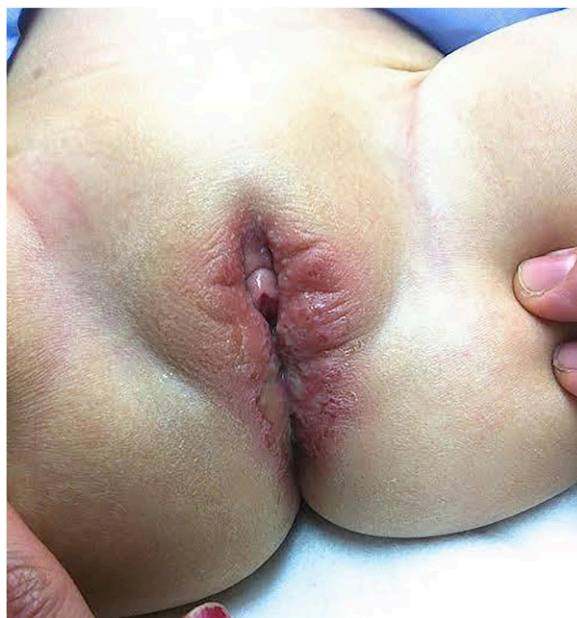


Figure 1. Ulcerated genital rash.

ulcerated lesions measuring 1.5 cm wide with erythematous bases and tiny blisters with serous fluid in the genital and perianal regions (Fig 1). The rash is foul smelling and tender to palpation. There is no lymphadenopathy.

Laboratory evaluation reveals the complete blood cell count and serum electrolyte levels to be within the reference range. Cultures of the blood and lesions are sent to the

laboratory. The Gram-stain is negative. The culture and direct fluorescent antibody (DFA) results confirm our diagnosis.

The Case Discussion and Suggested Readings appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/4/216>.

DISCUSSION

The patient's DFA test result was reported to be positive for herpes simplex virus (HSV) 1 in 24 hours, and her HSV culture results came back positive in 3 days. The tests confirmed our suspicion of a primary herpes infection based on the history of a sibling with a recent cold sore that had frequent physical contact with the child. The patient also had atopic dermatitis diffusely and scratched herself, which may have led to breaks in the skin and provided opportunity for inoculation. The child abuse medical team was consulted on this patient. After a thorough investigation of the family and of the evidence, they concluded that there had not been any evidence of abuse given the probable route of transmission from the sibling and the infant having no current or past injuries. She was treated with a 10-day course of oral acyclovir.

Differential Diagnosis

Diaper dermatitis is a common skin condition in infants and is usually caused by irritation from excessive moisture, yeast infection, or an allergic reaction to substances such as diaper dyes. Other possible diagnoses for rashes in the diaper region include seborrhea, atopic dermatitis, impetigo, scabies, psoriasis, and infections with cytomegalovirus, herpes virus, pinworm, and varicella virus. Seborrhea causes greasy patches of scaly skin in the inguinal region and is often found in other areas as well. Atopic dermatitis rarely occurs in the diaper region because the diaper tends to trap moisture in. Impetigo can develop when there is a break in the skin and can appear as tiny raised yellow fluid-filled vesicles and honey-colored crusted lesions. An autoimmune process such as psoriasis can present as reddened patches primarily in the diaper region without the distinctive silver scale and can cause concern for nonaccidental trauma. Other systemic autoimmune processes to consider when evaluating perianal ulceration are conditions such as Kawasaki disease and Crohn disease. Scabies can present in the diaper region with a widespread red, raised, itchy rash where the mites have burrowed in the skin, and it often affects multiple family members at the same time. Jaquet dermatitis is a severe form of contact diaper dermatitis that presents as pruritic nodules and ulcers in the genitalia of children with chronic diarrhea and incontinence and can be difficult to treat.

The Condition

After the neonatal period, infants usually acquire HSV (1 or 2) from direct skin-to-skin contact with someone with an active lesion, either a caregiver or from abuse. Most primary HSV infections during the period of childhood are asymptomatic, and shedding can occur in saliva without clinical disease. In

childhood, gingivostomatitis is the most common presentation of HSV and can be accompanied by the characteristic painful ulcerative or clustered oral and perioral vesicles on an erythematous base, fever, irritability, poor appetite, and adenopathy. Primary herpes is usually more severe than recurrent herpes. Blisters or ulcers can occur on any part of the body, and autoinoculation can happen anywhere. Children often contract herpetic whitlow by autoinoculation from finger sucking when they have orofacial herpetic infection. Children with eczema are more prone to acquiring herpes due to breaks in the skin. Eczema herpeticum is a rare but severe infection that occurs when HSV vesicles become concentrated at the sites of skin damage usually in patients with atopic dermatitis. Rarely, HSV can lead to Stevens-Johnson syndrome. The incubation period of HSV is usually 2 days to 2 weeks, and the sores of a primary infection last 1 to 3 weeks.

Diagnosis and Treatment

Gram-stain and culture can identify secondary bacterial infections. Potassium hydroxide testing of scrapings from the rash can identify a fungal infection. To diagnose HSV, viral testing is standard. The vesicle must be unroofed, and the lesion's base must be swabbed. The sensitivity of viral culture is low and declines rapidly as lesions crust and heal. Polymerase chain reaction assays for HSV DNA are more sensitive than cultures. The DFA staining of vesicular scraping is a rapid diagnostic test to accompany viral culture but is less sensitive than viral culture.

Treatment is primarily supportive. Despite painful oral lesions, children should be encouraged to drink fluids to prevent dehydration. In immunocompetent patients, there are limited data available on the efficacy of antiviral agents on the course of primary mucocutaneous HSV infection. However, our patient was treated with an antiviral agent in an attempt to decrease the duration of her symptoms. Exposed lesions can be covered with a dressing to prevent infection risk to others. Oral HSV infection is common in children, and they should not be prevented from attending school. Contact with newborns or those with eczema or immunosuppression should be avoided until the sores are healed. The prognosis is good, with lesions healing in 2 to 4 weeks.

Lessons for the Clinician

- Infants and toddlers usually acquire herpes simplex virus (HSV) from direct contact with someone with an active lesion.
- Treatment with antiviral agents is typically not warranted in immunocompetent hosts who acquire primary mucocutaneous HSV.
- Children who are not sufficiently mature to engage in consensual sexual activity who present with genital HSV

warrant a multidisciplinary child protection investigation to assess for sexual assault.

Suggested Readings

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Case 5: Ulcerated, Painful Genital and Perianal Rash in a 1-year-old Girl

Shwetha Chagalamarri and Anirudha Das

Pediatrics in Review 2018;39;216

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Index of Suspicion

4 Unexplained Fever in a 5-month-old Boy

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AUTHOR DISCLOSURE Drs Auriemma and Haberman have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 5-month-old previously healthy African American boy presents to the emergency department (ED) with an 8-day history of high-spiking daily fevers between 102°F and 104°F (38.9°C–40.0°C). On his second day of fever, he was diagnosed as having an acute suppurative otitis media by his primary care physician and was started on amoxicillin. Daily fevers continued despite adequate antibiotic compliance. Other than fever his only reported symptom is fussiness. Specifically, he has no cough, congestion, rash, vomiting, diarrhea, or change in appetite. In the ED his temperature is 103.1°F (39.5°C); heart rate, 175 beats/min; respiratory rate, 26 breaths/min; blood pressure, 98/64 mm Hg; and oxygen saturation, 98% on room air. He is ill-appearing and fussy but consolable. Subtle injection of the bulbar conjunctiva is present bilaterally without exudate. His heart rate is tachycardic, with regular rhythm and no murmur. His abdomen is soft and without organomegaly. His extremities are warm, well-perfused, and without edema. His lungs are clear to auscultation with normal respiratory effort. He has no rash or lymphadenopathy. The remainder of his examination findings are normal.

Laboratory values obtained in the ED reveal anemia with a hemoglobin level of 7.6 g/dL (76 g/L) and thrombocytosis with a platelet count of $486 \times 10^3/\mu\text{L}$ ($486 \times 10^9/\text{L}$). His white blood cell (WBC) count is normal, C-reactive protein level is elevated at 102 mg/L (971 nmol/L), and erythrocyte sedimentation rate (ESR) is elevated at 61 mm/h. Results of an electrolyte panel including liver enzymes, albumin, and renal function are normal. A urinalysis performed by bladder catheterization shows no sign of infection. Results of a respiratory viral panel obtained as part of an unexplained fever evaluation are negative. Chest radiography shows a normal cardiac silhouette and absence of pulmonary disease.

DISCUSSION

A key point before proceeding with a broad evaluation for fever of unknown origin is whether this patient needs to be promptly evaluated for Kawasaki disease (KD).

The classic diagnosis of KD requires at least 5 days of fever and at least 4 of the 5 principal features: extremity changes (erythema and/or induration of the palms or soles, periungual desquamation), polymorphous rash, bilateral nonexudative bulbar conjunctivitis that is often limbus-sparing, cervical

lymphadenopathy greater than 1.5 cm, and changes of the lips, tongue, and/or oral mucosa (red/cracking lips, oropharyngeal erythema, strawberry tongue). (1) Note that these features are not always present at the same time; therefore, historical report both by caregivers and previous health-care providers is meaningful. A significant portion of patients (15%–36%) (2) do not present with full classic criteria yet are at risk for complications of KD. An algorithm endorsed by the American Academy of Pediatrics and the American Heart Association for incomplete KD provides guidance for patients who fulfill the fever requirement but have only 2 or 3 principal features. For these patients an ESR and C-reactive protein should be obtained, and if systemic inflammation is present further supplemental lab criteria should be pursued. This includes evaluating for age-based anemia, hypoalbuminemia (albumin level ≤ 3 g/dL [≤ 30 g/L]), elevated alanine aminotransferase level, thrombocytosis (platelet count $\geq 450 \times 10^3/\mu\text{L}$ [$\geq 450 \times 10^9/\text{L}$] after 7 days of fever), leukocytosis (WBC count $\geq 15,000/\mu\text{L}$ [$\geq 15 \times 10^9/\text{L}$]), and sterile pyuria (≥ 10 WBCs per high-power field). (1)

Our patient has only 1 clinical feature (bilateral nonexudative conjunctivitis) and does not meet the classic criteria, and neither does he fall under the incomplete algorithm as described previously herein. However, it is important to note that there is an exception on the incomplete algorithm for infants 6 months of age or younger. In this age group, if an infant has fever for 7 or more days without a source, laboratory testing to evaluate for KD should be performed. If systemic inflammation is present, an echocardiogram is recommended even if no clinical criteria are present and regardless of the results of supplemental laboratory criteria. (1)

Patient Course

An echocardiogram performed on day 9 of fever revealed a moderate aneurysm of the proximal right coronary artery of 0.37 mm (Z score +7), diffuse ectasia of the proximal left anterior descending artery of 0.30 mm (Z score +6.6), and a prominent circumflex artery. The patient was given a 2-g/kg single infusion of intravenous immunoglobulin (IVIg) and was started on high-dose aspirin (100 mg/kg per day). He continued to have fever 36 hours after completion of IVIg and was given a second infusion of IVIg on day 12. His fevers returned approximately 48 hours after completion of the infusion. He was then given 30 mg/kg of IV methylprednisolone on day 16. A follow-up echocardiogram was obtained at this time that showed that the proximal right coronary artery aneurysm increased by 0.08 mm, the ectasia of the proximal left anterior descending artery remained

unchanged, and the circumflex artery became moderately enlarged. A new small (0.34-cm) aneurysm of the left main coronary artery also developed. At this time, a dose of infliximab (5 mg/kg) was given in addition to his 2-day corticosteroid course. He had no further fevers after a single dose of infliximab. Repeated echocardiograms 2 and 5 days after infliximab therapy showed stabilization of the size of his cardiac aneurysms. Computed tomography angiography of his chest, abdomen, and pelvis was negative for other signs of vasculitis or aneurysms. After more than 96 hours of being afebrile, he developed a new fever several days after receiving infliximab. Because infliximab can increase susceptibility to bacterial infections, further evaluation for possible infection was pursued. His fever was attributed to a *Klebsiella* urinary tract infection ($>100,000$ colony-forming units). He was treated with ceftriaxone, and fevers promptly resolved. He was discharged from the hospital on low-dose aspirin.

One month after discharge all of his coronary arteries returned to normal size. Owing to the severity of his initial presentation, he remained on aspirin therapy for 12 months.

The Condition

Young infants with KD are more likely to present with few or no classic features (3) and are at increased risk for coronary artery aneurysms. (4) Even infants diagnosed and treated within the first 10 days of fever have an increased incidence of coronary artery changes at the time of first echocardiogram, with some studies reporting rates as high as 43%. (4)(5) Of those with normal coronaries at the time of the first echocardiogram, more than 25% developed coronary changes even after appropriate treatment. (5) Therefore, high clinical suspicion in this age group is crucial to minimize morbidity.

Management

Typical treatment of KD involves high-dose aspirin plus IVIg as first-line treatment, with a second dose of IVIg given if the patient continues to have fever more than 36 hours after the initial dose. If fever persists after the second dose, potential therapies include corticosteroids, infliximab, other immunomodulators, and plasma exchange. (6) Disease that is IVIg resistant is associated with higher rates of coronary artery aneurysms. (7) Multiple predictive models have been developed to identify potentially resistant patients before treatment failure. Scoring systems that have proved useful in Japanese populations have not been shown to be as sensitive in other populations. (8) However, with multiple studies in recent years showing high safety and efficacy of

infliximab for IVIg-resistant disease, (9)(10)(11)(12) some centers are adding infliximab early in the disease course for known high-risk populations, such as young infants and patients who already have coronary artery dilation or aneurysm at the time of diagnosis. (5)

Lessons for the Clinician

- Evaluate for Kawasaki disease (KD) in all infants younger than 6 months with fever for more than 7 days without other explanation, regardless of the absence of clinical criteria.

- Infants younger than 6 months with KD frequently present with coronary artery changes or develop changes despite appropriate treatment.
- Infliximab is a safe and effective second-line treatment for intravenous immunoglobulin-resistant KD and is emerging as a potential adjuvant therapy for high-risk patients such as infants and those who present with coronary artery changes.

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1 Unilateral Leg Pain and Difficulty Walking

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EDITOR'S NOTE

We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: <https://mc.manuscriptcentral.com/pir>.

AUTHOR DISCLOSURE Drs Shah, Diaz-Medina, and Chen have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 5-year-old boy presents with unilateral leg pain and difficulty walking for 6 days. During that time, the patient developed a fever and an upper respiratory tract infection. Physical examination shows no edema, erythema, or warmth in the lower extremities. There is tenderness to palpation of the right lower extremity (RLE). There is also pain on passive and active range of motion (ROM) testing as well as decreased muscle strength in the RLE. The right patellar and Achilles reflexes are absent. The left lower extremity, however, shows unaffected ROM and muscle strength testing, with the patellar and Achilles reflexes diminished to 1/4+. When prompted to walk, the patient limps and is unable to bear weight on his RLE. Findings on radiographs of the hips and RLE and magnetic resonance images (MRIs) of the hips are all normal. Lumbar puncture shows a normal white blood cell count with an increased protein level, as well as elevated immunoglobulin G (IgG) levels. The MRI of the thoracic and lumbar spine shows abnormal enhancement of ventral and dorsal nerve roots extending off the conus and filum terminale into the cauda equina (Fig 1). In addition, there is particularly asymmetrical enhancement of the right dorsal nerve roots versus the left in the lumbar spine (Fig 2). Nerve conduction studies show axonal polyneuropathy in the bilateral lower extremity nerves tested and borderline decreased conduction velocity (abnormal findings

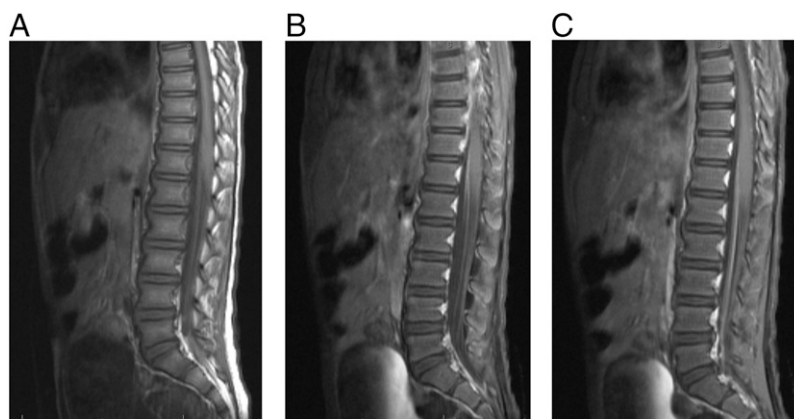


Figure 1. Sagittal T1 magnetic resonance images (A) without contrast and (B and C) with contrast. Abnormal enhancement of the ventral and dorsal nerve roots extending off the conus and filum terminale into the cauda equina can be seen.

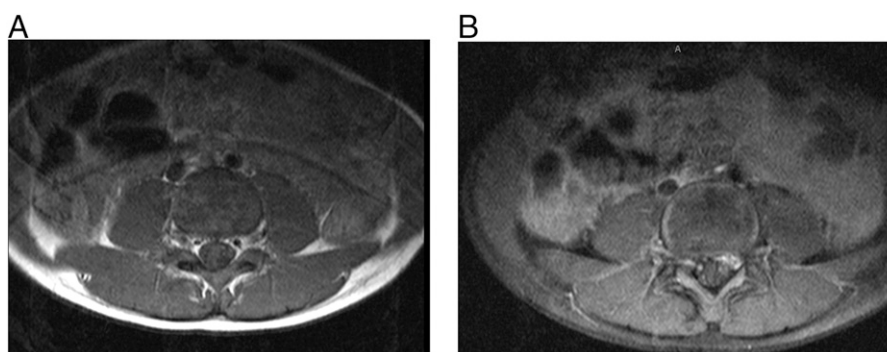


Figure 2. Axial T1 magnetic resonance images (MRIs) (A) without contrast and (B) with contrast. Particularly, asymmetrical enhancement of the right dorsal nerve roots versus the left can be seen in the MRI with contrast.

TABLE 1. Motor Peripheral Nerve Conduction Study

| NERVE | mA-ms | DML, ms | DML, mm | DMA, mV | NCV, m/s | NORMAL DML, ms | NORMAL DMA, mV | NORMAL NCV, m/s |
|----------------|---------|---------|---------|---------|----------|----------------|----------------|-----------------|
| Left peroneal | 100/0.2 | 4.1 | 60 | 1.7 | 45.8 | 6.5 | 2 | 44 |
| Right peroneal | 100/0.2 | 5.1 | 60 | 0.4 | 42.3 | 6.5 | 2 | 44 |

DMA=distal motor amplitude, DML=distal motor latency, NCV=nerve conduction velocity.

TABLE 2. Sensory Peripheral Nerve Conduction Study

| NERVE | mA-ms | DSL, ms | DSL, mm | DSA, μ V | NCV, m/s | NORMAL DSL, ms | NORMAL DSA, μ V | NORMAL NCV, m/s |
|-------------|----------|---------|---------|--------------|----------|----------------|---------------------|-----------------|
| Left sural | 94/0.2 | 1.9 | 60 | 24.3 | 34 | 4.4 | 6 | 40 |
| Right sural | 16.4/0.2 | 2.0 | 60 | 12.8 | 34 | 4.4 | 6 | 40 |

DSA=distal sensory amplitude, DSL=distal sensory latency, NCV=nerve conduction velocity.

TABLE 3. F-Response Study (Indicates Conduction Block and/or Axonal Loss)

| NERVE | mA-ms | M-LATENCY, ms | F-WAVE LATENCY, ms | NORMAL F-WAVE LATENCY, ms |
|----------------|---------|---------------|--------------------|---------------------------|
| Right peroneal | 100/0.2 | 5.1 | Absent response | ≤ 56 |

summarized in Tables 1-3). Electromyography testing finds positive waves and fibrillations and decreased recruitment. All of this testing together reveals the diagnosis.

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/1/36>.

DISCUSSION

The case illustrates a patient newly diagnosed as having Guillain-Barré syndrome (GBS) who atypically presented with unilateral leg pain. The ascending paralysis of GBS is classically bilateral and can be rapidly progressive, so diagnosis needs to be made promptly. Symptoms of GBS may include distal lower extremity weakness, cranial nerve involvement leading to facial muscle weakness, ataxia, muscular or radicular pain in the spinal region, symptoms of a preceding infection, and reduced tendon reflexes in the involved extremities. (1)(2) Progression of weakness can occur within a few hours to days, which is why swift diagnosis can prove to be crucial.

The diagnosis can be challenging, notably in children, atypical presentations, and patients reporting pain initially. Our patient fell into each of these categories. The patient reported limited ROM secondary to pain. It has been seen that pain can present in more than 44% of children with GBS. (2) Given this symptom, the differential diagnosis included trauma, such as a strain; inflammation, such as transient synovitis or juvenile rheumatoid arthritis; congenital conditions, such as hip dysplasia; infection, such as discitis, and more. The differentiation and physical examination finding that the patient's RLE difficulty was primarily weakness and not pain, combined with loss of deep tendon reflexes, is what led to performing a more complete neurologic examination.

Conditions that can be considered include poliomyelitis, acute flaccid myelitis, syringomyelia, acute disseminated encephalomyelitis, and more. Poliomyelitis is an infectious disease of the anterior horn motor neurons of the spinal cord and brain stem. Flaccid, asymmetrical weakness and muscle atrophy are common, thus the overlap in clinical presentation with this patient is clear. The polio-like acute flaccid myelitis can involve a febrile or respiratory illness before neurologic symptoms, similar to GBS. The Centers for Disease Control and Prevention (CDC) confirmed 277 cases of this pathologic condition from August 2014 to December 2016 alone. Manifestations include limb weakness or paralysis and variable cranial nerve involvement. Evidence of spinal gray matter lesions can be seen on MRI with this condition. (3) Syringomyelia involves the formation of a fluid-filled cavity or cyst in the spinal cord. Presentation can include chronic pain or loss of pain and temperature sensation, weakness, paralysis, or disruption to parasympathetic or sympathetic function. Acute disseminated encephalomyelitis is an immune-mediated demyelinating disease that is also often postinfectious. Manifestations include the systemic signs and symptoms of encephalopathy and can progress to pyramidal signs, hemiparesis, cranial neuropathy, and more. All of these pathologic conditions and

others were kept in mind during the neurologic evaluation, but we would find that GBS would be the prevailing diagnosis in the end.

Although GBS is a clinical diagnosis, further testing can be valuable for validation. On examination of the patient's cerebrospinal fluid, the classic GBS finding of cytoalbuminologic dissociation was present, as well as increased IgG levels. It has been shown that IgG levels in cerebrospinal fluid may be elevated in patients with GBS; one of the disease variants, acute motor axonal neuropathy, involves antiganglioside antibodies, which are IgG in class. (4)(5)

The patient's postcontrast MRI showed the typical GBS findings of surface thickening and contrast enhancement on the conus medullaris and nerve roots of the cauda equina. (6) More commonly in GBS, this enhancement is of the ventral nerve roots, but as with our patient it can also be seen dorsally. Nerve conduction studies are essential for classification between variants of GBS, such as acute motor axonal neuropathy or acute inflammatory demyelinating polyneuropathy. Findings from these studies can show overlap of the variants, as with our patient.

The general treatment protocol for GBS includes hospital admission and intravenous immunoglobulin, 400 mg/kg per day for 5 days, or plasma exchange. If there is a treatment-related fluctuation, which is deterioration after initial stabilization or improvement, repeated treatment with the same course should be used. During acute presentation, monitoring of respiration, swallowing difficulties, progression of weakness, and autonomic dysfunction is paramount. Disease severity and duration vary in patients and can range from minor weakness with spontaneous recovery to quadriplegia and ventilator dependency without signs of improvement for months or longer. Approximately 20% to 30% of those with GBS progress to respiratory failure and need to be placed in an ICU for ventilation. (1)(2) Autonomic dysfunction can include systemic hypertension, widely fluctuating blood pressures, arrhythmias that can require pacemaker placement, ileus, or bladder paralysis. Mortality occurs from these complications, and in Europe and North America it ranges from 3% to 7% of patients with GBS. Emergencies arise most often when diagnosis is delayed, particularly in young children. Patients with GBS often have enduring ailments, such as fatigue and pain, due to lasting axonal loss, and these can have a marked effect on quality of life. Unfortunately, approximately 20% of patients with GBS cannot walk unaided 6 months after disease onset. (1)

In summary, GBS has the potential for major morbidity and mortality. With this patient, it was important to perform a careful and thorough physical examination to establish a

broad differential diagnosis that included GBS. Because of the diagnostic difficulty due to the patient's atypical presentation, it was important to evaluate the patient with a lumbar puncture, MRI, and nerve conduction studies.

Lessons for the Clinician

- Symptoms of Guillain-Barré syndrome (GBS) may include distal lower extremity weakness, cranial nerve involvement leading to facial muscle weakness, ataxia, muscular or radicular pain in the spinal region, symptoms of a preceding infection, and reduced tendon reflexes in the involved extremities.
- Diagnosis is clinical and can be challenging, notably in children, atypical presentations such as those with unilateral symptoms, and patients reporting pain initially. Differential diagnoses include poliomyelitis, acute flaccid myelitis, syringomyelia, acute disseminated encephalomyelitis, and more.
- Lumbar puncture, magnetic resonance imaging, and nerve conduction studies can help bolster the diagnosis.
- The general treatment protocol for GBS includes hospital admission and intravenous immunoglobulin, 400 mg/kg per day for 5 days, or plasma exchange.

- Because the ascending paralysis of GBS can be rapidly progressive and cause respiratory failure and/or autonomic dysfunction, diagnosis and treatment need to be performed promptly.

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Case 1: Unilateral Leg Pain and Difficulty Walking

Samir Shah, Gloria Diaz-Medina and Joshua Chen

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Pediatrics in Review

An Official Journal of the American Academy of Pediatrics

Case 1: Unilateral Leg Pain and Difficulty Walking

Samir Shah, Gloria Diaz-Medina and Joshua Chen

Pediatrics in Review 2018;39;36

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The online version of this article, along with updated information and services, is located on the World Wide Web at:

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1 Vomiting and Ventricular Arrhythmia in a 2-year-old Girl

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EDITOR'S NOTE

We invite readers to contribute *Index of Suspicion* cases through the PIR manuscript submission system at: <https://mc.manuscriptcentral.com/pir>.

AUTHOR DISCLOSURE Drs Gern, Mehta, McCammond, Holmes, and Guzman-Cottrill have disclosed no financial relationships relevant to this article. Dr Gern's current affiliation is Department of Pediatrics, University of Washington, Seattle, WA. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 2-year-old girl presents to an urgent care clinic with a 1-day history of nonbloody, nonbilious vomiting, intolerance of oral intake, and decreased urine output. There is no present history of fever, abdominal pain, diarrhea, cough, trauma, or travel. Two weeks before presentation, she recovered from a febrile illness. In urgent care, she is treated with two 20-mL/kg normal saline boluses and intravenous ondansetron and is admitted to the general ward for monitoring and intravenous fluid rehydration.

On hospital admission she is afebrile, and vital signs include a heart rate of 106 beat/min and elevated blood pressure of 121/69 mm Hg. She is sleeping but awakens appropriately with examination. The rest of her physical examination findings are normal.

Her complete blood cell count shows a white blood cell count of 18,800/ μ L ($\times 10^9$ /L), with 85.1% neutrophils; a hemoglobin level of 10.5 g/dL (105 g/L); and a platelet count of 451 $\times 10^3$ / μ L (451 $\times 10^9$ /L). A comprehensive metabolic panel is notable for an aspartate aminotransferase level of 104 U/L (1.74 μ kat/L) (reference range, 5–43 U/L [0.08–0.72 μ kat/L]) but is otherwise normal (including normal electrolyte levels).

Four hours later, the patient is found pulseless and apneic. There is brief return of spontaneous circulation with cardiopulmonary resuscitation and epinephrine and sodium bicarbonate administration. Continuous electrocardiogram monitoring demonstrates ventricular tachycardia (VT) with deterioration to ventricular fibrillation (VF) (Fig). She continues to have multiple cardiac arrests with VT/VF requiring defibrillation, cardiopulmonary resuscitation, and, eventually,

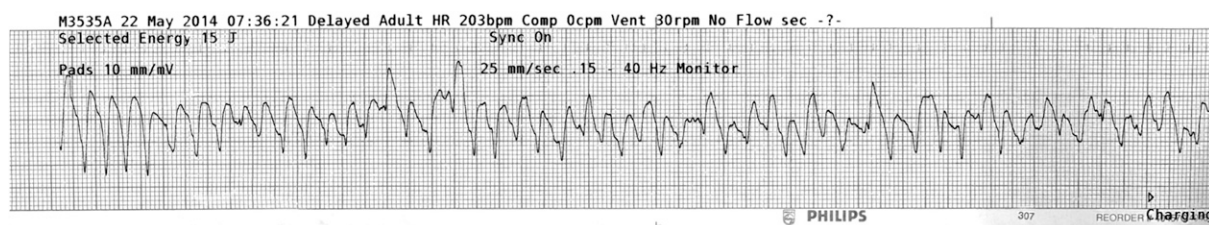


Figure. Continuous electrocardiogram monitoring showing ventricular tachycardia and fibrillation.

cannulation to veno-arterial extracorporeal membrane oxygenation. Cardiac imaging reveals the cause of her acute event.

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/2/91>.

DISCUSSION

Transthoracic echocardiogram revealed a normal-sized heart, moderate to severely depressed global biventricular function, and normal-appearing left ventricular size and thickness. There was no pericardial effusion. Notably, there was severe dilation of the left anterior descending coronary artery (5.9 mm, z+16) and right coronary artery (4.2 mm, z+7.2), with mild dilation of the left main coronary artery (3.2 mm, z+2.4). No blood flow was visualized in the distal coronary arteries.

On further questioning, it was discovered that 2 weeks before admission she was evaluated by her pediatrician on the fourth day of fever during that 11-day febrile episode. Her pediatrician documented mild bilateral conjunctival injection and oropharyngeal erythema. At that time, a urine sample demonstrated sterile pyuria. Based on this history she was diagnosed as having incomplete Kawasaki disease (KD) and subsequent coronary aneurysms, leading to myocardial ischemia and cardiovascular collapse.

The Condition

First described by Dr Tomisaku Kawasaki in 1967, KD is a well-described systemic vasculitis and the most common cause of acquired pediatric heart disease in the developed world. Clinical features include a temperature of 100.4°F or higher ($\geq 38.0^{\circ}\text{C}$), bilateral nonpurulent conjunctivitis, oral mucosal inflammation, polymorphous rash, extremity changes of the hands and feet, and cervical adenopathy. The acute febrile phase generally lasts 10 to 12 days and is self-limited. If untreated during the acute phase, KD can lead to cardiac complications in 15% to 25% of affected individuals. Complications may include coronary artery aneurysms (CAAs) and potentially fatal coronary insufficiency, myocardial ischemia, and infarction.

The formation of CAAs in KD is a direct result of the inflammatory process. On days 7 to 9 of illness, there is a neutrophil infiltration into the coronary artery walls that is quickly replaced by monocytes, lymphocytes, and IgA plasma cells. This response causes fragmentation of the elastic lamina and damage to the media, resulting in aneurysm formation. As the acute inflammation recedes, these areas of remodeling can undergo fibrosis and scar formation. Risk factors that increase a patient's risk of developing CAA include delay of intravenous immunoglobulin (IVIG) administration past the 10th day of illness, persistent fever after IVIG administration, elevated inflammatory markers, a white blood cell count more than $12,000/\mu\text{L}$ ($12 \times 10^9/\text{L}$), anemia, hyponatremia, thrombocytopenia, hypoalbuminemia, male sex, and younger than 12 months.

Differential Diagnosis

This patient's initial presentation was thought to be consistent with acute viral gastroenteritis. Rarely, viral gastroenteritis can proceed to cardiovascular collapse in the setting of extreme volume depletion, potassium disturbances, or acid/base disturbances, none of which were present in this patient. Before the echocardiogram, viral myocarditis and underlying cardiomyopathy were high on the differential diagnosis. The presentation of recalcitrant VT/VF is extremely rare in children and broadened the differential diagnosis to include congenital abnormalities of myocardial conduction, such as Brugada syndrome, long QT syndrome, and catecholaminergic polymorphic ventricular tachycardia. The recurrence of ventricular arrhythmias in an otherwise healthy child can also suggest myocardial ischemia and coronary insufficiency. The additional history of an 11-day febrile illness with 2 of 5 associated clinical criteria of KD and supplemental laboratory findings (white blood cell count, anemia, sterile pyuria, aspartate aminotransferase level elevation) were instrumental in increasing the suspicion of KD.

Management

In 2004, the American Heart Association published guidelines for the management of KD. Treatment in the acute phase includes high-dose IVIG (2 g/kg) and high-dose oral aspirin (80–100 mg/kg per day). Ideally, treatment should be administered within the first 10 days of fever.

No data exist from randomized controlled trials to aid in directing treatment when coronary manifestations are observed on initial presentation. When coronary aneurysms are present, IVIG and aspirin are still administered. Dipyridole or clopidogrel are often added for increased antiplatelet effect. When giant or rapidly expanding coronary aneurysms are present, warfarin and/or heparin therapy may also be considered. The American Heart Association KD guidelines state that the usefulness of corticosteroids in initial treatment is not well established. (1) However, corticosteroids are often used for patients who are refractory to IVIG plus oral aspirin. A retrospective Japanese study demonstrated that children who received IVIG plus prednisolone for first-line IVIG nonresponders had a lower risk of failing to respond compared with the IVIG group. (5)

Once the patient develops coronary thrombus or evidence of cardiac ischemia, the previously described treatment may provide some benefit, but more invasive procedures must be considered. Percutaneous transluminal coronary balloon angioplasty can be used to relieve mild to moderate stenosis, although there is a relatively high rate of restenosis (25%).

Other more advanced interventions, such as stent placement, percutaneous transluminal coronary rotational ablation, and percutaneous transluminal coronary revascularization, have shown promising results in small sample sizes, although these techniques are frequently limited by patient size.

Our patient was treated with IVIG and methylprednisolone owing to the severity of her clinical presentation and coronary artery disease. In addition, she was anticoagulated with heparin while undergoing veno-arterial extracorporeal membrane oxygenation. However, she died of complications related to anticoagulation.

Lessons for the Clinician

- Consider Kawasaki disease in febrile children with any manifestations of Kawasaki disease, including children with only 1 or 2 clinical features.
 - Consider acute cardiac disease or myocardial ischemia in patients with recalcitrant ventricular arrhythmias who do not improve with the pediatric advanced life support algorithm.
 - Kawasaki disease should be highly considered in pediatric patients with acute cardiac disease/myocardial infarction.
- Kawasaki disease should be considered as a cause of ventricular fibrillation, especially in young children, where it is especially rare.

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4 Weakness and Headaches in a 14-year-old Boy

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AUTHOR DISCLOSURE Drs White, Liu, and Das have disclosed no financial relationships relevant to this article. Dr White's current affiliation is Pediatrics Residency Program, University of Las Vegas School of Medicine, Las Vegas, NV. Dr Liu's current affiliation is Department of Internal Medicine, University of Arizona College of Medicine-Tucson, AZ. Dr. Das's current affiliation is Pediatric Hospitalist, Duke University School of Medicine, Durham, NC. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 14-year-old boy presents to the hospital with headache and weakness for the third time in 3 months. One day before hospital admission the patient developed a severe headache that resolved with sumatriptan use. Hours before arriving at the hospital he played basketball for half an hour outside, but on returning home he noticed a worsening throbbing right-sided frontal headache without radiation. Within a few minutes the patient developed progressively increasing weakness in all 4 extremities, which prompted him to lie down. His previous presenting symptoms had included fever, headache, dizziness, blurry vision, stumbling gait, and stiffness, muscle tightness, and a tingling sensation in all 4 extremities. At previous presentations, acute disseminated encephalomyelitis (ADEM) and migraines were suspected, and the patient was started on high-dose (1 g per 24 hours for 5 days) intravenous methylprednisolone, with a prednisone taper, to which he responded very well and symptoms (headaches, dizziness, weakness, ataxia) resolved.

The child was in good health until 3 months ago. His medical history is significant for intermittent asthma, triggered by weather changes, which is well controlled with albuterol and mometasone as needed. Immunizations are up to date. The patient's family moved into a new house approximately 8 months previously. Because the previous owner had many parrots, the house was uninhabitable due to the amount of bird feces, which the patient and his father had to clean before moving in. He has not traveled in the previous 3 years. He was born and raised in Las Vegas, Nevada. He eats home-cooked food that is healthy and well balanced.

Findings from physical examination are benign for the patient. On neurologic examination he is alert and oriented. Cranial nerves II to XII are intact. His sensory and motor function is intact in all extremities. Romberg sign is positive. However, there were no other signs of cerebellar involvement or gait abnormalities present.

DISCUSSION

A range of differential diagnoses was considered for the headache and weakness, including atypical migraine, multiple sclerosis, ADEM, and meningitis.

Brain magnetic resonance imaging (MRI) was performed and was compared with his brain MRI from the previous week. This was a follow-up MRI with the neurologist 3 months after treatment for ADEM. The report is unchanged from

the previous brain MRI that showed numerous foci of increased flair and deep white matter to bilateral cerebral hemispheres clustered in frontal and parietal white matter suspicious for demyelinating disease. Findings on MRI of the spine were not significant. He had an interventional radiology-guided lumbar puncture with opening pressure of 16.8 cmH₂O and a cerebrospinal fluid (CSF) cell count showing 1 white blood cell and no red blood cells, with protein and glucose levels elevated at 7.9 g/dL (79 g/L) and 1,838 mg/dL (102 mmol/L), respectively. The CSF Gram-stain showed no white blood cells or organisms, and the culture was negative. Cryptococcal antigen in CSF was positive. Other infectious evaluations performed, including CSF *Aspergillus* antigen, *Coccidioides* antibody, acid-fast bacillus culture, and fungal culture, were all negative. India ink stain was negative for yeast cells. Serum testing included human immunodeficiency virus antigen/antibody assay negative, cytomegalovirus immunoglobulin (Ig) M negative and IgG positive, *Mycoplasma pneumoniae* antibody negative, IgM negative, and *Toxoplasma* IgM/IgG negative.

With the history of admission and treatment for ADEM, the patient underwent some immune evaluations. Laboratory tests performed included T-cell subsets, CD4 T helper cell subsets, and quantitative immunoglobulins, and the results were all within normal limits. An autoimmune panel had negative findings for antinuclear antibodies, anti-DNA, anti-Jo, anti-SSA/b, anti-Sm, and scleroderma antibody, whereas anti-RNP was mildly elevated. Rheumatoid factor level was within normal limits. The multiple sclerosis panel was negative, and myelin basic protein was within normal limits.

With the laboratory results returning positive for cryptococcal antigen in the CSF as well as white matter lesions on brain MRI, these findings are consistent with cryptococcal central nervous system disease in an otherwise immunocompetent patient. Subsequently, antifungal therapy with intravenous amphotericin B liposome and oral flucytosine is started. The patient was to have repeated CSF studies performed after 2 weeks as per the infectious disease specialist. On repeated CSF testing, culture was negative, fungal culture and India ink staining were negative, and the cryptococcal antigen was negative as well.

THE CONDITION

Cryptococcus neoformans is an encapsulated, yeastlike fungus that is round to oval and approximately 4 to 6 μ m in diameter. The yeast has a thick capsule that consists of polysaccharides that protect the fungus from phagocytosis. It is an opportunistic fungus that typically affects patients who are

immunocompromised especially those that are HIV positive. *C neoformans* is commonly found in soils visited by birds. It is transmitted via inhalation and deposits in the alveoli causing a range from asymptomatic to progressive pulmonary disease. Symptoms usually have a subacute/chronic course and can include chronic cough, low-grade fever, chest pain, mucoid or bloody sputum, malaise, and weight loss. Due to *C neoformans* affinity for the CNS, it commonly spreads hematogenously to the brain and is the most common cause of fungal meningoencephalitis. Most patients with cryptococcosis of the central nervous system present with signs and symptoms of subacute meningitis, such as headache, irritability, meningismus, fever, cranial nerve palsies, visual disturbances, altered mental status, or seizures over several weeks.

There have been isolated cryptococcomas of the central nervous system that have been previously described in immunocompetent adults. There was 1 similar case report in an immunocompetent child and an infant found in the literature.

DIAGNOSIS

Testing for detection of cryptococcal polysaccharide antigen in serum and CSF is highly specific and more sensitive for diagnosis of invasive disease compared with microscopy and culture. We used the enzyme immunoassay for detection of cryptococcal capsular polysaccharide antigen, which, according to Redbook, the antigen is detected in CSF or serum specimens from more than 98% of patients with cryptococcal meningitis. The MRI shows intraparenchymal lesions. One can expect there to be growth on the fungal culture as well as an elevated white blood cell count with lymphocyte predominance and an elevated protein level. There is often an elevated opening pressure of the CSF greater than 200 cmH₂O. An India ink stain can help visualize the polysaccharide capsule. It appears as a clear halo around the yeast in a black field.

TREATMENT

Standard treatment includes a combination of amphotericin B and flucytosine. The additive effects of this combination has allowed for a decreased amount of amphotericin needed to treat, therefore reducing its toxicity on the patient while also preventing resistance associated with monotherapy. A standard induction dose for liposomal amphotericin B (AmBisome, Astellas Pharma US, Northbrook, IL) and amphotericin B lipid complex at 3 to 6 mg/kg per day have shown treatment successes similar to that of amphotericin B deoxycholate, with reduced toxicity. Our hospital had liposomal amphotericin B available for treatment of our

patient. In discussion with the infectious disease and neurology specialists, the team treated the patient with standard induction therapy of amphotericin B and flucytosine for 2 weeks followed by 8 to 10 weeks of fluconazole.

Lessons for the Clinician

- This case was reported to highlight the importance of thorough history taking and critical thinking of

differential diagnoses in the presence of unique symptoms.

- This patient gives us a look into an immunocompetent pediatric patient and reminds us that cryptococcal meningitis can occur in immunocompetent children as well.

Suggested Readings for this article are at <http://pedsinreview.aappublications.org/content/39/8/424>.



1 Abdominal Distention in a 2-month-old Boy

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EDITOR'S NOTE

Has 2019 been perfect? Even amidst good times, we often face challenges. Some of the challenges are because we battle structures and systems that just weren't made perfectly, and sometimes we face challenges of imperfect processes. This month, the *Index of Suspicion* cases (and some of the other articles in this issue) deal with structural and biochemical (process) problems. Enjoy!

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

A 2-month-old full-term boy with normal prenatal ultrasonography findings and an unremarkable birth history presents to the emergency department with several days of forceful, nonbloody, nonbilious vomiting and worsening abdominal distention. His oral intake and urine output are decreased. His history is significant for gastroesophageal reflux, but he is developing well.

On examination he appears ill. His vital signs are significant for hypertension (blood pressure, 160/90 mm Hg) and tachypnea with shallow breathing. He has a distended abdomen and mottled extremities. The physical examination findings are otherwise normal. He has not had fevers, rash, swelling, or changes in his stools.

An abdominal radiograph reveals no evidence of obstruction or intra-peritoneal free air. Ultrasonography of the abdomen shows moderate ascites. There is no pyloric stenosis. The liver and spleen are normal in size. There is mild hydronephrosis of the left kidney and a large subcapsular collection that is compressing the renal parenchyma. The bladder wall appears thickened.

His complete blood cell count shows a platelet count of $924 \times 10^3/\mu\text{L}$ ($924 \times 10^9/\text{L}$). A complete metabolic panel shows a low sodium level of 125 mEq/L (125 mmol/L), an elevated potassium level of 6.9 mEq/L (6.9 mmol/L), a blood urea nitrogen level of 44 mg/dL (15.7 mmol/L), and a creatinine level of 1.5 mg/dL (132.6 $\mu\text{mol/L}$). Findings from liver function tests and urinalysis are normal. He is admitted to the PICU for monitoring and further management of his renal failure.

On arrival at the PICU he is intubated for worsening respiratory distress. A paracentesis drain is placed, and ascites fluid is sent for analysis, which leads to the diagnosis.

AUTHOR DISCLOSURE Drs Haddad and Gangadharan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE 1. Differential Diagnoses for Ascites

| ETIOLOGY OF ASCITES | SUGGESTED LABORATORY TESTING OF ASCITIC FLUID |
|--|---|
| Congestive hepatopathy (cirrhotic and noncirrhotic, including heart failure) | Albumin (to calculate serum-to-ascites albumin gradient) |
| Peritoneal infection or inflammation | Culture and cell count with differential count |
| Biliary or pancreatic ascites (traumatic or nontraumatic) | Bilirubin, lipase, and amylase levels |
| Genitourinary disorders (ie, obstructive uropathy) | Creatinine +/- urea levels |
| Chylous ascites | Triglyceride level and cell count with differential count |
| Malignancy | Protein, cytology, and tumor markers |

DISCUSSION

Biochemical analysis of the clear yellow peritoneal fluid suggested that it was a transudate. The fluid creatinine level was moderately elevated, suggesting that the fluid was urinary in origin. Urinary ascites should be considered after more common causes of transudative ascites have been ruled out. In this case, there was no hepatomegaly noted on ultrasonography, lessening the likelihood of suprahepatic obstruction (Budd-Chiari syndrome), cardiac issues, or storage disease. Nephrotic syndrome must also be considered, but this patient had no proteinuria.

An ascites creatinine to serum creatinine ratio greater than 1.0 is highly suggestive of an intraperitoneal urine leak, whereby urine accumulates as free fluid in the peritoneal cavity. The most common cause of urinary ascites in neonates is congenital obstructive uropathy. Downstream obstruction causes increased pressure in the kidney, which leads to the perinephric extravasation of urine. This is compared with acquired cases that occur later in life usually due to complications of pelvic surgery if the bladder or ureters are inadvertently injured.

A urology consult was obtained and the patient was sent for a voiding cystourethrogram, which showed a dilated posterior urethra, spontaneous vesicoureteral reflux into a tortuous and dilated left ureter, hydronephrosis, and subsequent visualization of contrast in the subcapsular collection on the left, likely from a lower pole fornix. These findings confirmed a diagnosis of posterior urethral valves. There was unilateral high-grade vesicoureteral reflux, with fornix rupture and a large perinephric urinoma that had also ruptured, causing urine to leak into the peritoneum.

The Condition

Posterior urethral valves are congenitally occurring membranous folds located in the posterior urethra that obstruct the outflow of urine from the bladder. They are the most common etiology of bladder outlet obstruction in male newborns. The bladder responds to the increased resistance by detrusor muscle hypertrophy, which leads to vesicoureteric incompetence or obstruction that causes reflux and hydronephrosis. The back pressure of urine in the renal collecting system may find a “pop-off” into the perinephric space.

This pop-off mechanism seems to initially protect the kidneys from the deleterious effects of elevated bladder pressures. However, with time the extrinsic renal compression from the urinoma can decrease perfusion to the compressed kidney, which causes hypertension and loss of renal function, a condition known as Page kidney. There are higher concentrations of creatinine and potassium in urinary ascites than in serum. These substances then diffuse into the blood, making the renal failure seem even worse.

Management

The patient’s creatinine concentration improved to baseline with slow drainage of the urinary ascites. On the third hospital day, he underwent a successful primary valve ablation via cystoscopy. The vesicoureteral reflux resolved, his kidney function improved, and his electrolytes normalized. He was discharged from the hospital on 1 medication for hypertension, which was later discontinued, and he is currently thriving.

Lessons for the Clinician

- Urinary ascites should be considered in the broad differential diagnosis of ascites, when more common causes

have been ruled out (Table 1). Laboratory testing of ascitic fluid should be performed along with other clinical investigations, such as a thorough history, physical examination, and possible imaging, in the evaluation of infants presenting with abdominal distention and ascites.

- The most common cause of urinary ascites in neonates is congenital obstructive uropathy, which causes increased pressure in the kidney that may “pop-off,” leading to the perinephric extravasation of urine. Posterior urethral valve (PUV) is the most common cause of obstructive uropathy in male infants.
- The presence of PUV may be suggested prenatally by ultrasonography findings. Bladder outlet obstruction can lead to distention of the bladder and proximal urethra (the “keyhole” sign) that could suggest the

presence of PUV, but these findings may also be absent either because the obstruction is mild or because routine anatomy ultrasonography is performed too early in gestation (18–22 weeks). Hydronephrosis may or may not be present. Oligohydramnios is a late finding in severe cases.

- Patients, thus, often present postnatally with abdominal distention due to urinary ascites, but the condition should also be suspected in male infants with decreased urine output or difficulty voiding. PUV is diagnosed by voiding cystourethrogram, and the treatment is surgical ablation of obstructing valves.

Suggested Readings for this article are at <http://pedsinreview.aappublications.org/content/40/12/636>.

Suggested Readings

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Case 1: Abdominal Distention in a 2-month-old Boy

Diana Haddad and Sandeep Gangadharan

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1 Acute Respiratory Failure in a 1-month-old Girl

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EDITOR'S NOTE

It is good to be thankful. Whether in mindfulness training, historical contexts, or religious beliefs, the values of gratitude are widely espoused. Last month, readers in Canada celebrated a national day of Thanksgiving, and, this month, readers of *Pediatrics in Review* in the United States are celebrating Thanksgiving.

There is much for which to be thankful. Some gratefully celebrate personal blessings and accomplishments, while others are thankful for the provision of food, water, and shelter. Getting even more basic, we can be grateful for airways, breathing, and circulation. In this month's *Index of Suspicion* cases, we follow the thought processes of clinicians helping children with altered respiratory statuses. Continuing to update our medical knowledge and skills, we provide care for which our patients and their families can be grateful.

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

A 1-month-old girl presented to the emergency department with respiratory failure. She was a full-term infant born after an uncomplicated pregnancy and delivery requiring no resuscitation. At 30 hours of life she had a choking spell with a feed and was transferred from the maternal ward to the NICU. A chest radiograph was performed and showed vertebral body segmentation anomalies in the thoracic spine, clear lung fields, and a nasogastric tube in the stomach. An echocardiogram demonstrated an atrial septal defect, a ventricular septal defect, and a bicuspid aortic valve. Due to the multiple observed anomalies, further diagnostic testing was performed to evaluate for a unifying diagnosis or a genetic syndrome. These tests included an eye examination, renal and head ultrasonography, brain magnetic resonance imaging, upper gastrointestinal series, chromosomal microarray, and karyotype; all results were normal. Due to her choking, a swallow study was performed with occupational therapy and demonstrated aspiration of feeds of all thicknesses. She was discharged on digoxin, furosemide, and full nasogastric feeds.

AUTHOR DISCLOSURE Drs Glenn, Mackow, Shivapour, and Crowley have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Two weeks after hospital discharge she started coughing, which was worse when feeding or in a supine position. One coughing episode was associated with emesis and respiratory distress, and the family brought her to the emergency department. On arrival, she was in severe respiratory distress and required intubation. Examination was notable for tachycardia, 2/6 systolic murmur, decreased air entry with coarse breath sounds, hepatomegaly with liver edge 2 to 3 cm below the costal margin, pale skin, and capillary refill of 3 to 5 seconds. Respiratory failure continued to worsen and was accompanied by frequent desaturations requiring suctioning and manual positive pressure ventilation. Of note, suctioned secretions periodically resembled formula. She also had intermittent gastric distention despite appropriate positioning of the endotracheal tube (Fig 1). On rigid bronchoscopy she was found to have an H-type tracheoesophageal fistula (TEF) (Fig 2) and, thus, the diagnosis of VACTERL association was made. She underwent repair of the TEF; however, she died of complications related to her disease process.

DISCUSSION

The constellation of symptoms, including cyanosis during feeds, aspiration, abdominal distention with positive pressure ventilation, and suctioning of formula from the



Figure 1. Radiograph showing gastric distention.

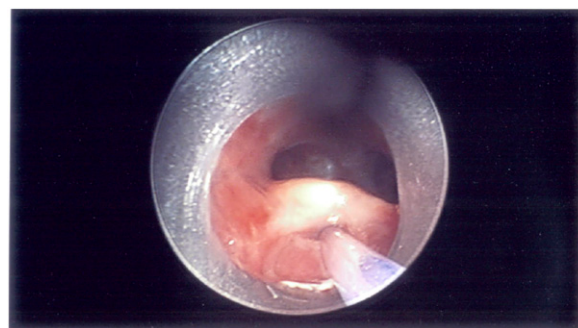


Figure 2. Findings on bronchoscopy.

endotracheal tube, were suspicious for an H-type (congenitally isolated) TEF. Previous radiographic studies demonstrated the nasogastric tube in the stomach, thus esophageal atresia was not present.

The esophagus and trachea develop from the primitive foregut at 4 to 6 weeks' gestation. A ventral diverticulum derived from the caudal part of the foregut forms the trachea and lung bud. The tracheoesophageal fold fuses into a septum that divides the foregut into the ventral laryngotracheal tube and the dorsal esophagus. (1) If this separation is incomplete, TEF results.

The most common type of TEF is esophageal atresia with distal TEF, which is typically diagnosed early in the neonatal period. (2) Congenital isolated TEF, also known as H-type or N-type, due to the downward angle of the fistula with the esophageal orifice inferior to the tracheal orifice, (3) is less common and composes 4% to 5% of all TEFs. (1) Presentation for this type of TEF includes a classic triad of symptoms: recurrent respiratory infections, aspiration during feeding with cyanosis, and abdominal distention. (3)(4) TEF is frequently associated with other anomalies, including cardiac, gastrointestinal, genitourinary, and musculoskeletal anomalies, and with genetic syndromes. (4) TEFs are usually diagnosed in the neonatal period because most cases are associated with esophageal atresia. However, isolated TEF frequently has a delayed diagnosis that is attributed to the subtlety of presentation, symptoms masquerading as other disease processes, and unsatisfactory diagnostic testing. (3)(4)

The constellation of vertebral defects, anal atresia, cardiac defects, TEF, renal anomalies, and limb abnormalities is known as VACTERL association. This is the most common constellation of defects associated with TEF, although affected infants have also been reported to have trisomy 13, 18, or 21; Pierre Robin sequence; 22q11 deletion syndrome; CHARGE (coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear

abnormalities) syndrome; Fanconi anemia; and polysplenia syndrome. (1) Diagnosing VACTERL requires 3 of these characteristic features, although patients may have other anomalies outside of this group. (1) TEF occurs in 50% to 80% of patients with VACTERL association. There is no specific genetic abnormality associated with VACTERL, and the association is thought to be the result of both genetic and environmental influences during development. The association is typically sporadic and does not have a clear inheritance pattern.

TEF has many associated complications, including recurrent pneumonia (which can lead to bronchiectasis if left untreated), acute lung injury and acute respiratory distress syndrome, lung abscess, poor nutrition, esophageal dysmotility, respiratory failure, and death. Overall survival is 80% to 90%, but this rate decreases when other congenital anomalies are present. Major postoperative complications include recurrent fistula and tracheal stenosis. Long-term complications include esophagitis, gastroesophageal reflux disease, Barrett esophagus, and hiatal hernia.

The diagnosis of TEF is made by a contrast tube esophagogram or rigid bronchoscopy. During a tube esophagogram, contrast is instilled into a catheter placed in the esophagus with the patient prone and in the Trendelenburg position. This allows contrast to flow “retrograde” through the angled fistula from the posterior esophagus to the anterior trachea. (1) This procedure carries the risk of respiratory compromise if a fistula is present. If the contrast evaluation is negative but clinical concern remains, or the patient is too unstable to have the contrast study, then rigid bronchoscopy with esophagoscopy is recommended. (5) Bronchoscopy is useful to delineate the anatomy of the TEF and assist in planning the approach for surgical repair.

Before repair, infants should be evaluated for other anomalies, including an echocardiogram to evaluate for congenital heart disease and determine aortic arch sidedness for surgical planning. Infants should be kept upright as much as possible. Gastric acid blockade should be instituted to reduce any injury from gastric secretions in the airway. (1) Primary repair is indicated in otherwise well infants. If repair is delayed due to low birthweight, pneumonia, or other anomalies or complications, patients should be kept on parenteral nutrition or a gastrostomy tube should be placed for feeding. (1) Ongoing mechanical ventilation after repair is associated with fistula recurrence and complications. Therefore, patients should ideally be weaned off mechanical ventilation before repair if the patient’s clinical condition permits.

Lessons for the Clinician

- Consider a diagnosis of congenital isolated tracheo-oesophageal fistula (TEF) in infants with recurrent pneumonia, coughing with feedings, or abdominal distention.
- Consider TEF in a neonate with aspiration and vertebral anomalies.
- The initial diagnostic test is typically tube esophagography, but the diagnosis can also be made with rigid bronchoscopy and esophagoscopy.
- Consider VACTERL association in patients who present with any type of TEF.
- Diagnostic tests for congenital isolated TEF have a high rate of false-negatives; if clinical suspicion persists, repeat diagnostic evaluation.

References for this article are at <http://pedsinreview.aappublications.org/content/40/11/590>.

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Sudden Bilateral Lower Extremity Weakness and Urinary Incontinence in a 13-year-old Girl

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EDITOR'S NOTE

I spent a week with medical students and family medicine residents in northeast Africa earlier this year. There, bright, clinically astute trainees at a major university use *Pediatrics in Review* as a core foundation of their pediatric curriculum. Wherever you are in the world this month, may these *Index of Suspicion* cases help you advance your knowledge and practice of pediatrics.

Philip R. Fischer, MD

Associate Editor, *Index of Suspicion*

PRESENTATION

A 13-year-old girl presented to the emergency department with acute onset of lower extremity weakness. She first awoke with dizziness but soon developed severe back pain, bilateral lower extremity pain and numbness, slurred speech, and inability to move her lower extremities or ambulate.

She reports having a 2-day history of headaches and back pain. Due to worsening of her symptoms, she went to an urgent care center the previous day. A rapid viral test showed she was influenza positive, and she took 2 doses of oseltamivir before admission. The patient had an upper respiratory tract infection approximately 2 to 3 weeks ago. In the emergency department, the patient is unable to void spontaneously despite being able to at home, and a urinary catheter is placed.

On physical examination her vital signs are as follows: temperature, 98.6°F (37.0°C); heart rate, 77 beats/min; respiratory rate, 20 breaths/min; and blood pressure, 119/74 mm Hg. Her BMI was within the 75th to 85th percentile. Her lower extremities bilaterally had 1/5 strength, diminished sensation to pinprick and temperature, and 0/5 patellar reflexes. She also had a 0/5 right Achilles reflex but a 1/5 left Achilles reflex. Her upper extremity strength, sensation, and reflexes were intact. Examination of her back showed no spinal tenderness to palpation or erythema. The rest of the physical examination findings were normal. Initial laboratory findings were normal, including complete blood cell count, complete metabolic panel, C-reactive protein level, creatine phosphokinase level, lactate level, and urinalysis. Polymerase chain reaction for common upper respiratory tract infection pathogens as well as cerebrospinal fluid (CSF) cultures were negative. CSF studies showed a white blood cell (WBC) count of 1/μL (0.001 × 10⁹/L), a red blood cell count of 0 × 10⁶/μL (0 × 10¹²/L), a protein level of 0.015 g/dL (0.15

AUTHOR DISCLOSURE Drs Cai and Bhise have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. Dr Cai's current affiliation is Children's Hospital at Montefiore, The Bronx, NY.

g/L), and a glucose level of 53 mg/dL (2.9 mmol/L). Magnetic resonance imaging (MRI) of her brain and spinal cord with contrast was normal.

DISCUSSION

Despite the normal CSF findings, there was concern for a treatable condition such as Guillain-Barré syndrome, so intravenous immunoglobulin (IVIG) was initiated for 5 days. Electromyography (EMG) with nerve conduction studies (NCSs) was performed and demonstrated normal motor and sensory unit action potentials with normal latencies, amplitudes, and conduction velocities but significantly reduced recruitment of motor unit action potentials (MUAPs) bilaterally, worse on the right leg. This indicated a possible demyelinating motor neuropathy, and a regimen of 1 g of methylprednisolone daily for 5 days was added. Subsequent examinations demonstrated mixed upper (UMN) and lower (LMN) motor neuron findings. Her bilateral diminished lower extremity strength and sensation improved dramatically, left slightly more than right. Her right patellar and left Achilles reflexes became brisk, and her left patellar and right Achilles reflexes remained absent. She also developed crossed adductor reflexes and a positive left Babinski sign. The absent or diminished reflexes in the left patella and right Achilles indicated an LMN process, and the brisk reflexes in the right patella and right ankle, crossed adductor reflexes, and positive Babinski sign indicated a UMN process. The patient's muscle tone was consistently normal. Repeated MRI studies 3 days after admission demonstrated new spinal cord lesions spanning from T6-7 down to the conus medullaris (Fig 1) with bilateral symmetrical T2 signal changes limited to the anterior gray matter (Fig 2).

Findings from further infectious, autoimmune, and metabolic evaluation were also negative or normal: serum human immunodeficiency virus, Epstein-Barr virus and CSF enterovirus, mycoplasma, and herpes simplex virus polymerase chain reaction; antinuclear antibodies, anti-double-stranded DNA, anti-SS-B, anti-myelin oligodendrocyte glycoprotein, and Lyme antibodies; CSF oligoclonal bands and immunoglobulin G index; serum vitamins B₁₂, D, and E; biotinidase; erythrocyte sedimentation rate; copper; and zinc. Test results were positive (after IVIG treatment) for anti-SS-A, human T-lymphotropic virus types 1 and 2, and mycoplasma immunoglobulin G antibodies.

DIFFERENTIAL DIAGNOSES

Possible conditions that the patient could have experienced can be split into 2 categories (1): peripheral (acute



Figure 1. Sagittal view of the spinal cord with T2-weighted images showing the abnormal T2 signal spanning from T6-7 down to the conus medullaris (arrows). A. T2 weighted sagittal image of the patient's mid-clavicular to mid-lumbar spinal cord. B. T2 weighted sagittal image of the patient's mid-lumbar to sacral spinal cord.

polyneuropathy, acute radiculoneuropathy [eg, Guillain-Barré], acute anterior poliomyelitis, acute flaccid myelitis) and central (acute transverse myelitis, acute flaccid myelitis, multiple sclerosis, neuromyelitis optica, subacute combined degeneration of the spinal cord, Wilson disease, infectious myelitis, cauda equina syndrome, lumbosacral neuritis, spinal stroke).

THE CONDITION

Acute flaccid myelitis (AFM) is a rare neurologic disease of unknown etiology. Despite numerous studies implicating enterovirus-68 (EV-68) and other polioviruses as the cause, none have been definitively established to date. Currently, the Centers for Disease Control and Prevention (CDC) defines a confirmed case of AFM as having 1) acute onset of focal limb weakness *and* 2) an MRI showing a spinal cord lesion largely restricted to gray matter spanning 1 or more spinal segments. A probable case of AFM has 1) acute onset of focal limb weakness *and* 2) CSF with pleocytosis (adjusted WBC count $>5/\mu\text{L}$ [$>0.005 \times 10^9/\text{L}$]). (2)

This disease mostly affects children and adolescents who present with polioliike symptoms. (3) It can be preceded by a prodromal febrile illness with respiratory and gastrointestinal symptoms a few days in advance. (3)(4) The most

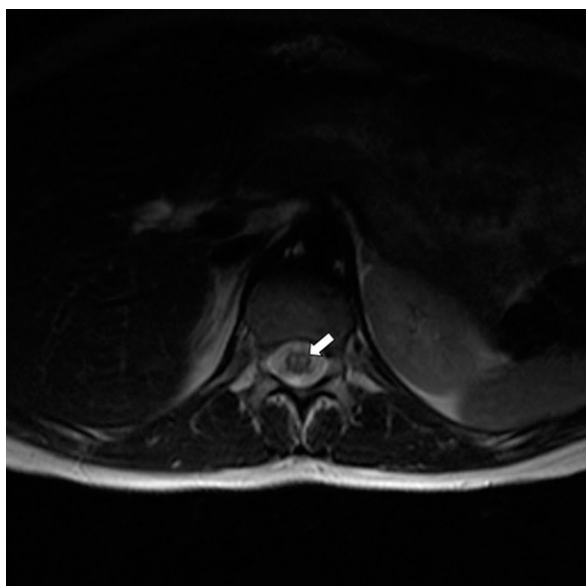


Figure 2. Tranverse view of the spinal cord with a T2-weighted image showing abnormal T2 signals localized in the bilateral anterior horn cells (arrow).

common respiratory symptoms include rhinorrhea, cough, and sore throat, and the most common gastrointestinal symptoms are vomiting or diarrhea. (5)(6) During the acute phase of the disease, patients mostly complain of fever, headache, neck pain, or pain around the affected limb. (3)(4) Neurologic findings include upper or lower limb weakness, sensory deficits, bladder or bowel dysfunction, hyporeflexia in the flaccid limbs, and varied cranial nerve dysfunction. (3)(4)(5)(6) Limb involvement includes 1 to all 4 extremities, more commonly the upper extremities, in an asymmetrical manner, with weakness ranging from paralysis to mild weakness. (3)(5)(6) The progression of neurologic symptoms can occur quickly, from a few hours to a few days. (6)(7)

Diagnostic studies such as MRI, lumbar puncture, and NCS/EMG can provide further evidence of the disease. MRI of the brain and spine reveals abnormal T2 signals localized to the anterior horn cells of the spinal cord correlating to the neurologic symptoms. These lesions can occur throughout the spine as well as in the dorsal pons and medulla. (8) Early MRIs of the spinal cord may be normal, and repeated imaging is required. (6)(7)(8) Early imaging may also show lesions throughout the gray matter that may be accompanied by edema. (8) Because the disease targets the anterior horn cells of the spinal cord, patients typically have LMN findings, but surrounding inflammation in the spinal cord leads to concomitant UMN findings. Analysis of the CSF often showed pleocytosis with a lymphocytic predominance. Although pleocytosis was not found in our patient, various case reports and reviews found the median WBC count to be

approximately 43 to 44/ μ L ($0.04 \times 10^9/L$), but the CDC notes a higher median count of 163/ μ L ($0.16 \times 10^9/L$). (5)(6)(9)(10) Studies also found elevated CSF protein levels (>45 mg/dL [>450 g/L]; reference range, 15–45 mg/dL [150–450 g/L]) but normal glucose levels (reference range, 40–80 mg/dL [2.2–4.4 mmol/L]) in most patients. (5)(6)(9)(10) NCS/EMG performed in multiple case reports and series noted reduced compound MUAP amplitudes, recruitment of MUAPs, and denervation of affected muscles. (6)(11)(12) One study found that despite the decrease in MUAPs, sensory unit action potentials were unchanged. (11) Fibrillation potentials started appearing 1 week after the onset of symptoms. (6) These abnormal NCS/EMG findings persisted for months (>20 weeks). (6)

The presence of UMN and LMN symptoms, the characteristic MRI appearance, and the NCS/EMG findings led us to the diagnosis in this patient.

MANAGEMENT

Management of AFM is mainly supportive, but the patient's respiratory status must be monitored carefully. Cervical lesions can lead to respiratory distress, and various case series have reported patients having respiratory insufficiency requiring intubation. (4)(5)(6)(9)

No formal guidelines have been established to acutely treat AFM, but multiple case reports and series have used various combinations of IVIG, high-dose intravenous corticosteroids, and/or plasma exchange to treat patients to various levels of improvement. (5)(6)(9)(10) There is no clear evidence or studies performed that prove that those therapies are either harmful or helpful for AFM treatment. (4) Furthermore, because of the unknown pathophysiology of the disease, the role of those therapies remains unclear. Corticosteroids are indicated for cord edema; however, it may worsen an active infectious process. (3)(4) IVIG is considered safe to use in most patients. Neutralizing antibodies against EV-68 have been found in commercially prepared IVIG. (4)(13) Plasma exchange can theoretically remove protective antibodies, which could worsen the disease process. (4) Fluoxetine has also been examined as a therapy for its antiviral effects against EV-68. (14) For long-term treatment, patients require physical and occupational therapy. Currently, the CDC is collecting CSF, blood, stool, and respiratory specimens from patients with possible AFM to search for potential causes.

The prognosis of this disease is variable. One study with median follow-up of 6 months found that all the children in the study had improved neurologic outcomes. All but 1 of the children still had residual motor deficits such as weakness, difficulty ambulating, and persistent need for a

ventilator. (7) Another study with follow-up of 1.5 to 3.0 months after discharge found that all the children had improved neurologic signs. Five of 9 patients had mild to no residual deficits, and the others still had deficits, including residual limb weakness. (10) In the case series examining the nationwide outbreak of AFM in 2014 (median follow-up, 4.2 months), 5% of patients reported complete recovery of strength and 18% were fully functional. Fourteen percent of patients were reported to be completely dependent on their caregivers. (9)

PATIENT COURSE

During her hospital stay, follow-up examinations demonstrated significant improvement in her lower extremity strength and sensation, return of specific reflexes, and resolution of urinary incontinence. The patient showed improvement during the IVIG infusion, but less so during the glucocorticoid treatment. The patient was transferred to an inpatient pediatric rehabilitation center for intensive physical and occupational therapy. At her latest outpatient evaluation, the patient was ambulatory with assistance.

Lessons for the Clinician

- Acute flaccid myelitis (AFM) is a rare polioliike neurologic disease of unknown etiology that typically has a prodromal period and presents as asymmetrical weakness of 1 to 4 limbs among other neurologic findings.
- Early magnetic resonance imaging (MRI) of the spinal cord may be normal, but repeated MRI shows abnormal T2 signals in the anterior horn cells in the spinal cord.
- Patients with acute AFM should have their respiratory status monitored closely in case of respiratory compromise.
- Although there is no evidence in terms of efficacy, case series have reported the use of intravenous immunoglobulin (IVIG), intravenous corticosteroids, and plasmapheresis. IVIG is considered a safe option.
- Cerebrospinal fluid, blood, stool, and respiratory samples from patients with possible AFM should be sent to the Centers for Disease Control and Prevention for further analysis and the local department of health contacted.

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Case 1: Sudden Bilateral Lower Extremity Weakness and Urinary Incontinence in a 13-year-old Girl

Raymond Cai and Vikram Bhise
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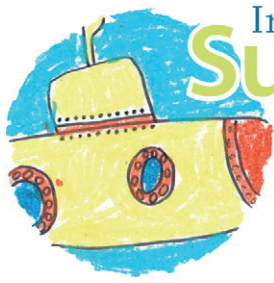
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Index of Suspicion

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A Medically Complex 10-month-old Boy with Lethargy

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EDITOR'S NOTE

We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: <https://mc.manuscriptcentral.com/pir>.

AUTHOR DISCLOSURE Drs Toce and Lyons have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 10-month-old boy status-post hematopoietic stem cell transplant for leukemia, with type IV renal tubular acidosis secondary to cyclosporine and resolved hypertension, presents to the emergency department with lethargy. He had been difficult to awaken since this morning. His family denies fever, other symptoms suggestive of infection, or trauma. Current medications include cyclosporine, sulfamethoxazole/trimethoprim, and citric acid. His family denies any possibility of unintentional toxic ingestion.

On examination he is lethargic, with a Glasgow Coma Scale score of 10 (eye opening = 2, verbal = 3, motor = 5). His temperature is 98.6°F (37°C), heart rate is 102 beats/min, respiratory rate is 22 breaths/min, and blood pressure is 84/35 mm Hg. The head is without signs of trauma. Pupillary examination is notable for miosis (2mm-1mm) bilaterally. A nasogastric tube is affixed to the right cheek. There is no meningismus. The chest, cardiac, and abdominal examination results are all within normal limits. The neurologic examination is notable for lethargy but without other focal deficits.

A complete blood cell count with a differential count reveals a white blood cell count of 5.6/ μ L (0.01×10^9 /L) (71% neutrophils), a hemoglobin level of 8.0 g/dL (80 g/L), and a platelet count of 129×10^3 / μ L (129×10^9 /L). Serum chemistry values (including calcium, magnesium, and phosphorous) are normal aside from a bicarbonate level of 19 mEq/L (19 mmol/L). A urine toxicology screen is negative for opiates, cannabinoids, benzodiazepines, barbiturates, and cocaine. Findings from a noncontrast head computed tomographic scan are within normal limits. Results of cerebrospinal fluid studies are all within normal limits. The patient is admitted to the hospital for further monitoring, and the diagnosis is made by an astute nurse.

DISCUSSION

The differential diagnosis of altered mental status in children is broad and includes infectious, neurologic, metabolic, traumatic, and toxicologic causes. The combination of altered mental status and miosis raised concern for a toxicologic etiology, but no exposure could be identified. However, on hospital admission a nurse performing her assessment noted the unusual appearance of the dressing used to affix the nasogastric tube. The dressing was removed and

found to be two 0.1-mg/day clonidine patches, which had been previously prescribed to treat hypertension. The family had mistaken the clonidine patches for a simple adhesive patch and placed them in the same bag they used to store nasogastric tube dressings. After their removal, the child was monitored and returned to his neurologic baseline within 24 hours. The exposure to clonidine was missed by the medication history that focused exclusively on medications taken orally.

Medication errors are common in pediatric inpatient settings. A prospective cohort study of pediatric inpatients found an error rate of 5.7 errors for every 100 medication orders. The most common error type was incorrect dose (28%), followed by incorrect route (18%). (1) The medical reconciliation is a type of medication history that is used to ensure that all of the patient's medications are accounted for and properly ordered when a patient is admitted to the hospital. Electronic medical reconciliation decreases admission medical reconciliation errors, with 1 study reporting a 53% reduction in nonintercepted errors. (2) An accurate medication history, including oral, topical, intranasal, and nonprescription medications, in addition to herbal supplements and vitamins, is necessary to reduce medication errors.

Clonidine exposure in this child could have been suspected based on the constellation of central nervous system (CNS) depression and miosis. Clonidine is used in children for the treatment of attention-deficit/hyperactivity disorder, Tourette syndrome, other behavioral conditions, sedation and withdrawal in the ICU, and hypertension. (3)(4)(5) Clonidine belongs to the imidazoline class of medications, which also includes guanfacine, dexmedetomidine, and tizanidine. It is available in liquid, pill, and transdermal (patch) preparations. Clonidine patches come in 2-, 5-, and 7.5-mg strengths, which release 0.1, 0.2, and 0.3 mg/day of clonidine, respectively. Patches are replaced every 5 to 7 days. Residual drug can remain in the patch even after removal, and cases of toxicity due to ingestion of a patch have been reported. (6)

The mechanisms by which clonidine induces sedation and lowers blood pressure and heart rate are incompletely understood. (7) Clonidine binds to presynaptic α_2 -adrenergic receptors in the locus coeruleus in the pons, producing sedation, and in the nucleus tractus solitarius in the medulla, leading to a decrease in norepinephrine release, which contributes to the decrease in heart rate and blood pressure. In addition to being an α_2 -adrenergic receptor agonist, clonidine binds to the imidazoline-1 receptor in the rostral ventrolateral medulla in the CNS and in the periphery. This binding produces a decrease in heart rate, blood pressure,

and myocardial contractility and is thought to be responsible for the cardiovascular adverse effects seen during clonidine administration and overdose. (8)

The use of clonidine in children is increasing. (9) As clonidine's clinical use has increased, so have unintentional pediatric exposures. (10) Between 2000 and 2011 there was a significant yearly increase in pediatric exposures to central α_2 -adrenergic receptor agonists (clonidine, guanfacine, and tizanidine) of nearly 6% per year. (11) In 2015, there were 3,938 cases of clonidine exposure in children younger than 20 years. (12)

The diagnosis of clonidine overdose/toxicity is a clinical one based on a detailed exposure history and physical examination. Symptoms of clonidine overdose are directly related to sympathetic depression and include lethargy and altered mental status, respiratory depression, bradycardia and hypotension, and miosis. (11) Paradoxically, early in exposure, patients can develop hypertension due to peripheral α -adrenergic receptor stimulation. (10) The constellation of symptoms associated with clonidine toxicity is sometimes mistaken for opioid toxidrome given the significant overlap in symptoms (miosis, respiratory depression, CNS depression). Providers should have a high index of suspicion for clonidine exposure in patients who present with CNS depression, bradycardia, and hypotension and have access to clonidine. Serum clonidine concentrations can be obtained, but results typically take several days, limiting their clinical utility. Similarly, standard urine drug testing will not detect clonidine.

Treatment of clonidine overdose includes supportive care with specific attention to the airway, breathing, and circulation. Respiratory depression should be treated with positive pressure ventilation. End-tidal carbon dioxide monitoring provides one mechanism for monitoring respiratory effort. Significantly obtunded children who are not protecting their airway should be intubated, although this is rare. Symptomatic bradycardia can be treated with atropine. Patients who are hypotensive should receive isotonic fluids. However, the need for vasopressor agents is uncommon. Decontamination with charcoal can be considered for children who present early after ingestion, presuming they are able to safely swallow and protect their airway. A careful skin examination should be performed, and any patches should be removed. Naloxone has emerged as a potential treatment for clonidine toxicity in children. Case reports have demonstrated improvement in mental status and respiratory effort in children receiving naloxone after clonidine exposure. (13)(14) A recent retrospective cohort analysis of pediatric clonidine exposures showed that naloxone reversed somnolence in 40 of 51 patients. (15) Asymptomatic children

should be observed in a monitored setting for 8 hours from the time of ingestion. Symptomatic patients should be admitted for overnight cardiopulmonary monitoring. Most children do well with good supportive care, and fatalities associated with clonidine use are extremely rare. (12)

Lessons for the Clinician

- As clonidine use in children and adults has increased, so have unintentional pediatric exposures.
- Clonidine formulations include patches, which may be missed by some medication histories.

- Clonidine overdose presents with central nervous system depression, respiratory depression, bradycardia, hypotension, and miosis.
- Treatment of clonidine overdose includes management of the airway, breathing, and circulation, including the use of atropine for bradycardia, as well as fluids for hypotension.
- Naloxone has been used with varying levels of success but should be considered in patients with severe, symptomatic clonidine overdose given its wide safety margin.

References for this article are at <http://pedsinreview.aappublications.org/content/40/2/79>.

Case 1: A Medically Complex 10-month-old Boy with Lethargy

Michael S. Toce and Todd W. Lyons

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1 Cardiac Arrest in a 2-month-old Boy with a Prenatal Course Complicated by Alloimmunization

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EDITOR'S NOTE

Children face a daily balancing act between antigens, allergy, and immunity. Sometimes, that balance turns pathologic. Either the antigen can “win” or the immune response can end up hurting the host. In the review articles and case reports this month, we are reminded of immune reactions gone awry, and we learn how to care for affected children.

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

A 30-year-old gravida 2, para 1 woman with an intrauterine pregnancy at 29 1/7 weeks' gestation was referred for suspected fetal anemia secondary to rhesus (D) (Rh[D]) alloimmunization. The fetus received 3 intrauterine transfusions (IUTs) during the pregnancy (Table). The patient delivered vaginally at 37 1/7 weeks' gestation. The birthweight was 2,680 g, and Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. On postnatal day 1, phototherapy was initiated for hyperbilirubinemia. On postnatal day 2, a complete blood cell count showed a white blood cell count of 2,500/ μ L (2.5×10^9 /L), a hemoglobin (Hb) level of 16.7 g/dL (167 g/L), a hematocrit level of 46.6%, and a platelet count of 68×10^3 / μ L (68×10^9 /L). The baby was discharged on postnatal day 3 when phototherapy was discontinued. Repeated bilirubin levels were within normal limits at an outpatient follow-up visit on postnatal day 4. The baby was seen in the clinic on postnatal day 10 for a health supervision visit, and a follow-up appointment was scheduled for 2 months of age.

On postnatal day 49, the parents noted the baby to be jaundiced, and they contacted the primary pediatrician, who instructed them to bring the child to the clinic later that week. However, on postnatal day 51, the baby was found to be apneic and cyanotic at home. On arrival by the paramedics, the baby was in pulseless electrical activity. Cardiopulmonary resuscitation (CPR) was initiated en

AUTHOR DISCLOSURE Drs Chang, Chon, Baskin, Nael, and Chmait have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE. Intrauterine Transfusions Performed During Pregnancy for the Treatment of Rhesus (D) Alloimmunization

| TRANSFUSION NO. | GESTATIONAL AGE, WK | HEMOGLOBIN, G/DL (G/L) | |
|-----------------|---------------------|------------------------|-----------------|
| | | PRETRANSFUSION | POSTTRANSFUSION |
| 1 | 29 2/7 | 6.9 (69) | 14.2 (142) |
| 2 | 31 2/7 | 8.4 (84) | 15.1 (151) |
| 3 | 34 2/7 | 8.7 (87) | 15.9 (159) |

route to the hospital, and spontaneous circulation returned after 60 minutes of CPR.

DISCUSSION

Hospital admission laboratory test results were consistent with severe metabolic acidosis (pH <6.5, bicarbonate <5 mEq/L [<5 mmol/L]) and pancytopenia (white blood cell count $1,100/\mu\text{L}$ [$1.1 \times 10^9/\text{L}$], Hb 1.5 g/dL [15 g/L], hematocrit 6.1%, platelet count $7 \times 10^3/\mu\text{L}$ [$7 \times 10^9/\text{L}$]). The patient was transfused 10 mL/kg of packed red blood cells (pRBCs) and was transferred to a PICU. On arrival at the PICU, the boy deteriorated again, requiring an additional 30 minutes of CPR, at which point his parents elected to discontinue resuscitative efforts given the grave prognosis.

Autopsy was performed. Microscopic examination of the bone marrow revealed normocellular marrow with trilineage hematopoiesis and approximately 90% cellularity (Fig. A and B). There was a relative erythroid hyperplasia (myeloid-to-erythroid ratio was estimated to be 1:3-4), which was consistent with a bone marrow response to ongoing hemolysis. Most erythroid precursor cells had arrest at the late normoblast maturation stage. The myeloid precursors showed extensive left-shifted maturation, with essentially no mature neutrophils visible. Adequate megakaryocytes were identified, with occasional immature forms. Additional findings were steatosis and panlobular iron deposition (3+) in the liver (Fig. C) consistent with a history of intrauterine transfusion, and extramedullary hematopoiesis and white pulp depletion in the spleen (Fig. D), suggestive of inadequate bone marrow erythropoiesis.

The Condition

Anemia in a 2-month-old infant can be due to hemolysis that is immune mediated or hereditary, blood loss, Hb abnormalities, exposure to toxins, infections, or, rarely, iron deficiency. We describe a case of immune-mediated hemolytic disease of the fetus and newborn (HDFN) due to Rh(D) alloimmunization that was successfully treated in utero with

serial transfusions, resulting in an uncomplicated birth but, unfortunately, ending with the baby's demise at 2 months of age secondary to complications of subsequent untreated severe anemia. The pathophysiology of HDFN results from a Rh(D)-negative mother being sensitized to Rh(D)-positive fetal RBCs and subsequently having transplacental passage of maternal anti-D immunoglobulin G (IgG) antibodies into the fetal circulation. The IgG antibodies then cause fetal and neonatal anemia from both destruction of RBCs and bone marrow suppression of erythropoiesis.

Once a common condition, HDFN dramatically reduced in incidence after the implementation of Rh(D) immunoprophylaxis, with an associated reduction in mortality from 46 per 100,000 births to 1.6 per 100,000 births. (1)(2) However, the success of prevention has resulted in current physicians having limited experience caring for these patients. This is compounded by the fact that newborns treated in utero appear healthy at birth, which may lead to a false sense of reassurance for both parents and physicians.

Management

Prenatal management of alloimmunization has been described extensively. (3) Maternal laboratory testing and serial fetal Doppler velocimetry of the middle cerebral artery peak systolic velocity can accurately identify the at-risk fetus. (4) The primary method to definitively diagnose fetal anemia is ultrasonography-guided sampling of the fetal blood. (5) Once anemia is confirmed, an IUT can be performed. (4) (5) IUTs are generally conducted at specialized fetal therapy centers. The procedure-related fetal loss rate is approximately 1%. (5)

The goals of immediate postnatal management in neonates with HDFN are focused on the identification and treatment of anemia and hyperbilirubinemia. Persistent or worsening postnatal anemia can be caused by several mechanisms of variable timing, so close postnatal surveillance for the first few months after birth is warranted. (6) (7)(8) Immediately after birth, the Hb level may be normal

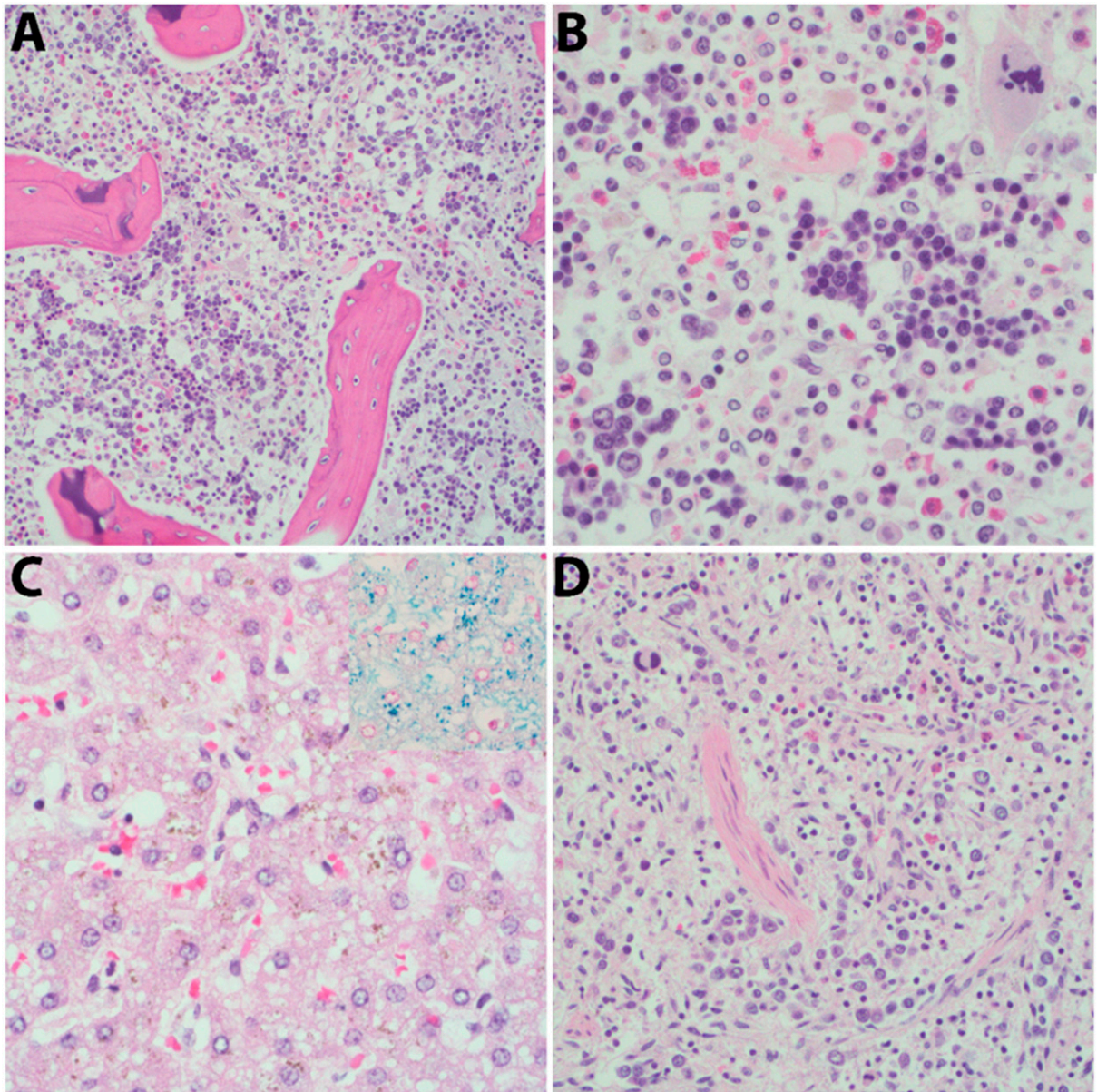


Figure. A and B. Microscopic examination of the bone marrow reveals normocellular bone marrow with trilineage hematopoiesis. There is a relative erythroid hyperplasia with predominance of normoblasts at different stages and decreased myeloid cells with left-shifted maturation (hematoxylin-eosin [H&E], original magnification $\times 100$ and $\times 200$, respectively). C. Section from liver shows macrovesicular and microvesicular steatosis with frequent intracellular and Kupffer cell hemosiderosis. Inset: Iron special stain. D. Section of spleen reveals extramedullary hematopoiesis and white pulp depletion (C and D: H&E, original magnification $\times 200$).

or mildly decreased, which may give the parents and the pediatrician a false sense of reassurance. However, in the coming days to weeks, the Hb level may drop significantly due to persistent maternal IgG circulating in the baby and destroying newly produced endogenous Rh(D)-positive RBCs. Maternal IgG antibodies causing hemolysis can persist for up to several months. An additional mechanism is hyporegenerative anemia, which may begin in utero and can persist for up to several weeks after delivery. (6)(9)(10)

The etiology of hyporegenerative anemia is unclear; however, immune destruction of RBC precursors, (11)(12) bone marrow suppression from IUT itself, (12) and erythropoietin deficiency (7)(8)(9)(13)(14) are implicated. Bone marrow suppression by IUTs remains controversial because bone marrow suppression has also been described even before the implementation of IUTs. (6)(7)(15) Some studies have shown that the rate of postnatal transfusions is increased in neonates who have received IUTs (77%–89%)

compared with neonates not treated with IUTs (27%–67%), (6)(7)(16) particularly during their first 6 months after birth. (7),(10)(17) Furthermore, there can be additional bone marrow suppression in the event of postnatal transfusions, which can be further compounded as the infant reaches his or her physiologic nadir at 6 to 12 weeks after birth. (6)(18)(19)

Considering that severe anemia can occur either early (≤ 1 week) or late (> 1 week to 6 months) after delivery, (6)(7)(8)(20) serial Hb monitoring after hospital discharge is crucial. The primary management of postnatal anemia is via transfusions of pRBCs. Up to 40% of infants require a pRBC transfusion for early-onset anemia and up to 80% will require at least 1 pRBC transfusion for late-onset anemia. (6)(7)(8)(20)(21) Other supplementary strategies to treat postnatal anemia include administration of erythropoietin, (22)(23) folic acid, (24)(25) and intravenous immunoglobulin. (8)(26)(27) Also, parents and pediatricians should be aware of and monitor for signs and symptoms of severe anemia, such as fatigue, difficulty with feeding, irritability, tachycardia, or paleness.

Hyperbilirubinemia occurs secondary to RBC breakdown due to circulating antibodies and should be promptly addressed to prevent progression to kernicterus. It is most commonly managed with phototherapy or exchange transfusion. (8)(16) Phototherapy increases the excretion of bilirubin products in the urine. An exchange transfusion filters the bilirubin and remaining maternal antibodies from the infant's peripheral blood and reduces the degree of hemolysis by providing immunologically compatible donor blood. (28)

In this case, the newborn status was optimized by serial fetal IUTs, which led to a false sense of reassurance of the

baby's status. Thus, subsequent development of anemia was not detected, causing the baby's demise at 2 months of age secondary to complications of untreated severe anemia. We recommend close follow-up with serial Hb levels for at least the first 3 months after birth or until the physiologic nadir occurs. (6)(18)(19)

Lessons for the Clinician

- Although the postnatal management of hemolytic disease of the fetus and newborn (HDFN) is not uniform, it is important for pediatricians to be educated on this matter because the resulting anemia and hyperbilirubinemia are both treatable morbidities.
- Strict postnatal surveillance for anemia is critical in HDFN-affected babies, including those who appear healthy, with normal hemoglobin levels immediately after delivery.
- Serial assessments for the development of anemia should be performed for at least the first 3 months after birth or until resolution of the physiologic nadir occurs. (6)(18)(19)
- The detection of jaundice in an infant with a known history of alloimmunization requires urgent medical evaluation, including a complete blood cell count and serum bilirubin concentration.
- The pediatrician should work in conjunction with a hematologist to ensure a safe postnatal course and follow-up to optimize outcomes for this treatable disease.

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**Case 1: Cardiac Arrest in a 2-month-old Boy with a Prenatal Course
Complicated by Alloimmunization**

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1 Delayed Diagnosis in a 13-year-old with Persistent Neurologic Symptoms after a Carnival Ride

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EDITOR'S NOTE

For some of us, summer offers time to get rejuvenated and refreshed so we can return with positive energy as we get back into the “flow” of patient care activities. The notion of flow was popularized a decade ago by Mihaly Csikszentmihalyi in the bestseller *Flow: The Psychology of Optimal Experience*. Satisfaction with daily experiences was said to best result when we mindfully engage in a flowing state of consciousness that provides creativity and enjoyment.

Similarly, physical health is impaired when organ systems are hindered from allowing body fluids to flow normally. This month's *Index of Suspicion* cases include examples of altered blood and intestinal flow. Enjoy working through interesting diagnostic thought processes.

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

A previously healthy 13-year-old girl presented to her local emergency department with headache, word-finding difficulty, and transient vision changes after a carnival ride. Results of a noncontrast head computed tomographic (CT) scan were normal, and she was discharged from the local emergency department.

Over the next 2 weeks her headache and intermittent word-finding difficulty persisted. She also developed paresthesia of the right hemibody and had trouble completing schoolwork. These symptoms prompted self-referral to a neurologist, who performed an electroencephalogram that was significant for left-sided slowing. The neurologist referred her to the hospital for further evaluation.

On arrival at our hospital her vital signs are normal and she is not experiencing neurologic symptoms. Her physical examination reveals a 2/6 systolic ejection murmur. She is neurologically intact, with no visual, motor, or sensory deficits. Coagulation studies, inflammatory markers, complete blood cell count, and electrolytes are within normal limits. The antinuclear antibody titer is moderately positive at 1:640. Findings from echocardiography with a bubble study are normal. Imaging studies lead to the diagnosis.

AUTHOR DISCLOSURE Drs Thompson, Wildman-Tobriner, and Parente have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

DISCUSSION

Before obtaining further imaging, the differential diagnosis was broad and included complex migraine, concussion, seizure, anxiety, transient ischemic attack, carotid artery dissection (CAD), electrolyte abnormalities, coagulopathies, and autoimmune disorders such as systemic lupus erythematosus and multiple sclerosis. Many of these disease processes can present with focal neurologic symptoms; however, given the proximity of her symptoms to the carnival ride, trauma was thought to be a main contributing factor and helped narrow the differential diagnosis.

CT angiography revealed smooth tapering of the extracranial left internal carotid artery (ICA) and absence of flow in the supraclinoid ICA (Fig 1A). These findings were concerning for CAD, which was confirmed by conventional cervicocerebral angiography (Fig 1B). Neurosurgery was consulted and recommended medical management with aspirin. Ultimately, it was thought that neck hyperextension from the carnival ride caused the dissection. Her neurologic symptoms were attributed to ischemic changes from ICA occlusion.

The Condition

CAD can lead to arterial narrowing, occlusion, and even ischemic stroke. (1) With an annual incidence of 3 per 100,000 in pediatric patients, CAD represents a major cause of stroke in children. (2) Most patients with CAD are boys aged 8 to 10 years, and the most common

mechanisms of injury include direct blunt trauma to the head or neck, intraoral injury, or forceful hyperextension of the neck. (2)(3) Less commonly, CAD is associated with more inconsequential mechanisms of injury, such as after exercise or sporting events, fitness video game practice, sneezing, sexual intercourse, waterskiing, or, as in this case, a carnival ride. (4)(5)(6)(7) A similar finding of an ICA dissection leading to ischemic stroke has been reported in a 4-year-old patient after a roller coaster ride. (8) Spontaneous dissection can be associated with underlying disease processes such as Marfan syndrome, Ehlers-Danlos syndrome, fibromuscular dysplasia, and osteogenesis imperfecta. (9) If no clear mechanism for dissection is identified, further evaluation may be warranted.

Because CAD is a rare phenomenon in children, general practitioners may not consider it when a patient presents with neurologic symptoms; however, early recognition and intervention has the potential to prevent serious morbidity, such as stroke or even death. (10) The most common presenting symptoms of CAD are headache and focal neurologic deficits consistent with stroke, such as aphasia, hemiparesis, ataxia, facial palsy, and somnolence. However, in some cases, physical examination findings may be normal. (11) Therefore, if a patient presents asymptotically after a high-risk mechanism of injury, further evaluation may be warranted. In addition, CAD should be considered even without an obvious high-risk mechanism of injury if there is an abrupt onset of focal neurologic symptoms after seemingly mundane head and neck movements.

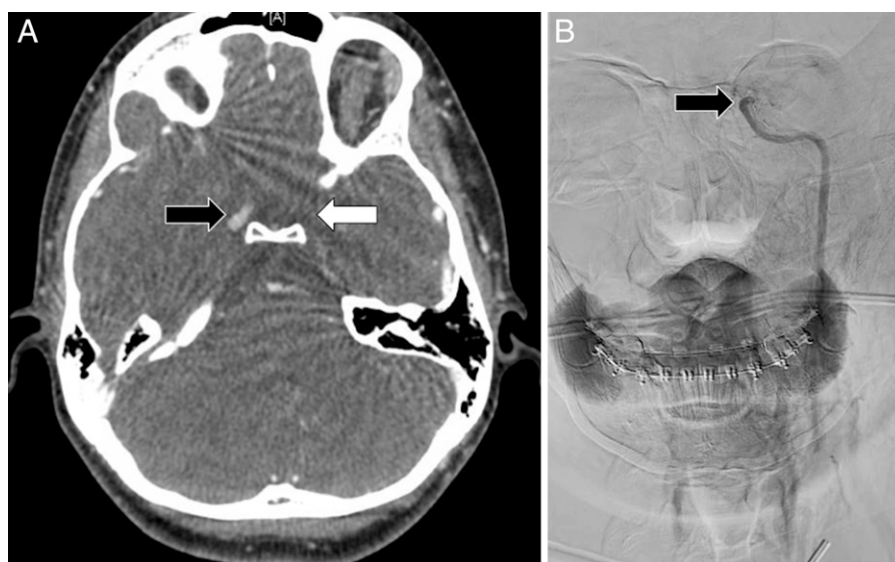


Figure 1. Imaging at the time of presentation. A. Computed tomographic angiogram showing nonopacification of the supraclinoid internal carotid artery (ICA) on the left (white arrow). Normal flow is seen on the right at the same level (black arrow). B. Digital subtraction angiogram. Injection of the left carotid artery shows delayed and diminutive flow throughout a narrowed left ICA, with abrupt tapering at the level of the ophthalmic artery (black arrow). No flow is seen in the middle cerebral artery or its branches.

If there is a high suspicion of CAD based on mechanism of injury and/or physical examination findings, the provider should immediately refer the patient for imaging at a hospital with neurosurgery available and consider starting antiplatelet therapy to prevent the occurrence or recurrence of stroke. (12)

Diagnosis and Management

Angiography is essential for diagnosis and is available in multiple forms. Conventional angiography remains the gold standard and also offers the option for treatment (stent placement). However, it is not without risk; some patients may develop neurologic deficits after angiography. (12) CT angiography allows for rapid imaging with accuracy close to conventional angiography and is typically widely available. Magnetic resonance angiography is another option but is not always appropriate in the acute setting and is less accurate than conventional angiography. Carotid ultrasonography with Doppler technique is another option, but visualization is often limited, and the study is operator dependent. (13)

Treatment for CAD consists of either antiplatelet or anticoagulation therapy to prevent the occurrence or recurrence of stroke. (14) Recurrence rates of stroke are similar between the two, and, thus, antiplatelet therapy is most commonly used because it requires less monitoring and has a safer pharmacologic profile. (12) Surgical and endovascular interventions, such as carotid angioplasty and stenting, are reserved for progressive or recurrent symptoms. (12)(14)

Patient Course

Our patient remained clinically stable throughout her hospital stay and returned to neurologic baseline without surgical intervention. She was started on aspirin (325 mg) daily and then transitioned to 81 mg of aspirin daily after 3 months. She will continue this for life. Imaging obtained 3 and 6 months after injury showed stable left ICA occlusion. Despite some reconstitution of blood flow from the posterior communicating artery, there was persistently diminished perfusion to the left middle and anterior cerebral arteries (Fig 2). She was able to resume sports 6 months after injury, and her school performance returned to baseline.

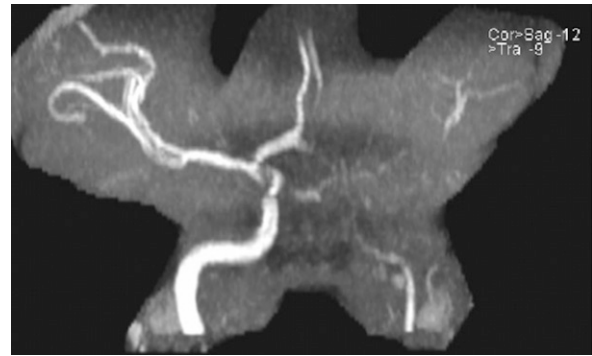


Figure 2. Magnetic resonance angiogram 6 months after the initial injury. Anterior maximum-intensity projection image shows persistent poor flow through the left internal carotid artery, with minimal flow in the anterior and middle cerebral arteries. Minimal reconstitution was via the posterior communicating artery.

Lessons for the Clinician

- The most common mechanisms of injury for carotid artery dissection (CAD) are direct blows to the head or neck, hyperextension of the neck, and intraoral injury.
- The most common presenting symptoms are focal neurologic deficits consistent with stroke, such as aphasia, hemiparesis, ataxia, facial palsy, and somnolence.
- CAD is diagnosed using angiography, whether computed tomographic angiography or conventional.
- Treatment for CAD is antiplatelet therapy or anticoagulation. Surgery is reserved for progressive or recurrent symptoms.
- If there is a high suspicion of CAD, the provider should immediately refer the patient for imaging at a hospital with neurosurgery available because early diagnosis and therapy can prevent the occurrence or recurrence of stroke.

ACKNOWLEDGMENT

The authors would like to thank Dr Eric Thompson, MD, for his expertise in interpreting neurologic studies and his management guidance.

This case is based on a presentation by Drs Thompson and Parente at the North Carolina Pediatric Society (NCPS) Annual Meeting, NCPS Resident Poster Session, Asheville, NC, Presentation Date: August 19, 2017, Poster Number: 1.

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Case 1: Delayed Diagnosis in a 13-year-old with Persistent Neurologic Symptoms after a Carnival Ride

Elizabeth J. Thompson, Benjamin Wildman-Tobriner and Victoria Parente

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1 Electrolyte Abnormalities in 7-day-old Girl

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EDITOR'S NOTE

While many of our patients are excitedly back in school this month, others are struggling to adjust to educational programs for their special needs, and others are getting used to medication regimens and having access to emergency medications. This month's *Index of Suspicion* cases all touch on endocrinology, but they also remind us of our need to adapt school and medication administration to maximize outcomes for all of our patients.

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

A newborn girl was admitted to the NICU for prematurity and respiratory distress. The mother's pregnancy had been complicated with gestational diabetes and preeclampsia with severe hypertension. After administering 2 doses of betamethasone to the mother to promote fetal lung maturation before delivery, the infant was delivered vaginally at 34.1 weeks' gestational age after labor induction. The mother, a 49-year-old woman (gravida, 4; para, 2) had a significant obstetric history, including 1 miscarriage, 1 stillbirth, and 1 healthy child with another partner. The current partner and father of this newborn had 1 healthy child from a previous marriage.

The current patient was a product of in vitro fertilization performed outside of the United States with a donor egg and the father's sperm. Preimplantation genetic testing was performed to detect aneuploidy of chromosomes 13, 18, 21, X, and Y. Prenatal care was administered outside of the United States until 27 weeks' gestational age; thereafter, the mother received obstetric care in the United States. Fetal ultrasonography at 34 weeks' gestational age yielded normal results.

At birth, the patient's weight was 1,790 g. Initially she received respiratory support with nasal continuous positive airway pressure. A chest radiograph was consistent with surfactant deficiency. The APGAR scores were 4 and 8 at 5 and 10 minutes, respectively. Because the maternal group B streptococcal status was unknown, the patient underwent a limited laboratory evaluation for sepsis, and empirical antibiotic drug therapy was initiated. The initial laboratory evaluation revealed a normal complete blood cell count and negative blood culture. On physical examination the patient was noted to have a port-wine stain on her right

AUTHOR DISCLOSURE Drs Kaminecki, Vates, Barrows, and Hudome have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

flank. Significant findings noted on genital examination included a prominent clitoris and prominent labia minora.

On the second day after birth the patient's sodium level was 141 mEq/L (141 mmol/L); the potassium level was not reported due to sample hemolysis. On the seventh day, the patient presented with hyponatremia (sodium level, 127 mEq/L [127 mmol/L]), hyperkalemia (potassium level, 9.8 mEq/L [9.8 mmol/L]), and elevated creatinine (0.96 mg/dL [84 μ mol/L]) and blood urea nitrogen (33 mg/dL [11.7 mmol/L]) levels. The elevated potassium level was attributed to sample hemolysis. The repeated potassium level was 10.2 mEq/L (10.2 mmol/L). The patient was also noted to have elevated calcium (13 mg/dL [3.2 mmol/L]) and phosphorus (8 mg/dL [2.5 mmol/L]) levels. An initial newborn screen for 57 diseases yielded normal results. Her blood sugar levels were stable, and her blood pressure and urine output were within the reference ranges. An electrocardiogram revealed PR and QRS intervals with normal durations and a normal T-wave amplitude. Nebulized albuterol and a single dose of kayexalate were initiated for hyperkalemia. Subsequent testing revealed the diagnosis.

DISCUSSION

After treatment with nebulized albuterol and kayexalate, repeated testing indicated a potassium level of 5.5 mEq/L (5.5 mmol/L) and a sodium level of 138 mEq/L (138 mmol/L). Physical examination and laboratory findings led to a suspicion of congenital adrenal hyperplasia (CAH). Pelvic ultrasonography revealed a normal uterus and left ovary, whereas the right ovary was not visualized; accordingly, karyotyping was ordered. Renal ultrasonography did not show any structural abnormalities. The patient was administered intravenous hydrocortisone and oral fludrocortisone for suspected CAH.

The results of blood testing indicated an elevated 17-hydroxyprogesterone level of 41,400 ng/dL (1252 nmol/L; reference range, 26–568 ng/dL [0.78–17 nmol/L]), elevated androstenedione level of 4,830 ng/dL (168 nmol/L; reference range, 50–449 ng/dL [1.7–15.6 nmol/L]), and elevated levels of 17-hydroxyprogesterone and testosterone; the patient also had a low aldosterone level and an elevated renin level. Serum karyotyping yielded a normal female karyotype of 46, XX. The laboratory findings were consistent with a complete 21-hydroxylase deficiency. Her second routine newborn screening was positive for CAH. The patient's genetic testing detected a mutation in the *CYP21A2* gene and confirmed the diagnosis of CAH. The patient continued to receive intravenous hydrocortisone and oral fludrocortisone and was started on oral sodium chloride.

A subsequent urologic evaluation identified a fused labia and vagina, with no obvious urethral opening noted on external examination. The patient's potassium level normalized to 5.1 mEq/L (5.1 mmol/L) on the third day after treatment initiation.

The Condition

CAH is among the most common inherited disorders, with an incidence of 1 per 15,000 live births. CAH is inherited in an autosomal recessive pattern, and more than 90% of such cases are caused by a 21-hydroxylase deficiency, the enzyme encoded by the *CYP21A2* gene. A 21-hydroxylase deficiency may present as the salt-wasting or simple virilizing form of classic CAH, or as “nonclassic” (late-onset) CAH. A 21-hydroxylase deficiency affects the conversion of 17-hydroxyprogesterone to 11-deoxycortisol, thus reducing the synthesis of cortisol and increasing the secretion level of corticotropin. Consequently, females exhibit increased production of androgens and virilization of the external genitalia. Although affected males appear normal at birth, scrotal hyperpigmentation and phallic enlargement may be observed. In addition, the salt-wasting form of CAH presents as an adrenal crisis, with hyponatremia, hyperkalemia, and failure to thrive.

Diagnosis

Routine newborn screening for CAH includes the measurement of 17-hydroxyprogesterone levels at 48 hours after birth, at which time most affected neonates have concentrations exceeding 3,500 ng/dL (105 nmol/L). However, screening for CAH is complicated by the fact that premature and low-birthweight newborns typically have higher 17-hydroxyprogesterone levels relative to full-term and normal-birthweight newborns. Given the potential risk of false-positive screening for CAH, the predictive value could be improved by adjusting the 17-hydroxyprogesterone cutoff values for both age and birthweight. Currently, 17-hydroxyprogesterone levels are adjusted only for the weight of the newborn in the state where our patient underwent screening.

The screening of premature newborns for CAH is further complicated by the administration of antenatal corticosteroid therapy for fetal lung maturation. Although a previous study found that long-term maternal corticosteroid treatment suppresses fetal 17-hydroxyprogesterone levels, the data regarding the effects of short-term maternal corticosteroid treatment on 17-hydroxyprogesterone levels remain limited. Therefore, a true-positive case of CAH may be missed because the potentially suppressive effects of corticosteroids can mask the relatively higher 17-hydroxyprogesterone level required for premature and low-birthweight

infants to achieve a positive screening result. This might explain our patient's negative newborn screening result. A positive CAH result during neonatal screening should prompt repeated testing of the patient's 17-hydroxyprogesterone level. Although a cosyntropin stimulation test is considered the diagnostic gold standard, this test is not required. A high level of 17-hydroxyprogesterone is also considered diagnostic for CAH. Patients with classic 21-hydroxylase deficiency may also exhibit a mineralocorticoid deficiency. Importantly, a decreased aldosterone level will result in a low sodium level and an elevated potassium level, which can cause cardiac arrhythmia.

Management

The treatment of CAH requires a multidisciplinary team approach. A newborn with ambiguous genitalia and suspected CAH should be evaluated by an endocrinologist, geneticist, and urologist. In addition, the parents should be provided with psychosocial support. For the patient, hydrocortisone is administered with the intent to generate sufficient levels of glucocorticoids and, thus, resolve excessive corticotropin secretion and hyperandrogenemia. Furthermore, fludrocortisone therapy and sodium chloride supplementation will help maintain mineralocorticoid activity and manage electrolyte abnormalities. An adrenal crisis in a patient with CAH requires urgent medical treatment with a bolus of normal saline and a stress dose of hydrocortisone.

Responses to management for CAH should be evaluated by measuring the 17-hydroxyprogesterone and androstenedione levels, renin activity, blood pressure, and growth velocity. Both infants and children with CAH are at risk for disease-related complications, such as adrenal crisis, as well as complications associated with the use of glucocorticoids, such as a decreased linear growth velocity, osteoporosis, and obesity.

Patient Course

In this case, the patient's electrolyte levels stabilized during her hospital stay; before discharge, she presented

with a potassium level of 5.0 mEq/L (5.0 mmol/L) and a sodium level of 139 mEq/L (139 mmol/L). She was subsequently discharged home on glucocorticoid replacement therapy with hydrocortisone and mineralocorticoid replacement with fludrocortisone and sodium chloride. At 14 months of age, the patient underwent surgical treatment including clitoroplasty and partial urogenital sinus mobilization vaginoplasty. Currently the patient is 19 months old and continues to take hormonal replacement therapy. Although the parents had received genetic counseling outside the United States before in vitro fertilization, they are not planning future pregnancies and, thus, did not receive further genetic counseling.

Lessons for the Clinician

- Girls with congenital adrenal hyperplasia (CAH) present with ambiguous genitalia, including clitoral enlargement and a common urethral-vaginal orifice. This condition may be difficult to diagnose in premature infants.
- Negative newborn screening does not exclude a diagnosis of CAH. Low-birthweight newborns and offspring of mothers treated with antenatal corticosteroids may receive false-negative screening results.
- The management of CAH includes lifelong glucocorticoid and mineralocorticoid replacement therapy. Females with a urogenital sinus may require reconstructive surgery.
- Couples often undergo in vitro fertilization procedures outside of the United States for various economic and social reasons; however, the quality standards for these procedures may not be as rigorous as those implemented in the United States. Clinicians should consider that some diseases are more prevalent in specific ethnic groups. For these reasons, a high index of suspicion should be maintained.

Suggested Readings for this article are at <http://pedsinreview.aappublications.org/content/40/9/482>.

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Case 1: Electrolyte Abnormalities in 7-day-old Girl
Inna Kaminecki, Thomas Vates, Frank Barrows and Susan Hudome
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Index of Suspicion

1

Intermittent Fevers, Persistent Vomiting, and Lethargy in a 3-year-old Boy

Archana Balamohan, MD,* Lorry G. Rubin, MD,* Peter Assaad, MD,[†]
Stefan H.F. Hagmann, MD, MSc*

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EDITOR'S NOTE

Last month, we thought globally, and *Index of Suspicion* included 4 cases of conditions that are more common outside of North America than they are within the United States. This month, 2 of the review articles focus on mycobacterial infections that can present anywhere in the world. Our cases include children with symptoms suggestive of mycobacterial infection, but some of these children ended up having different problems. Enjoy thinking through these cases!

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

A 35-month-old boy with a history of speech and slight motor delay is transferred to our institution with a 1-month history of intermittent fever and a 2-week history of vomiting. During this time he was noted to have poor appetite and a change in personality progressing to lethargy and generalized weakness. In addition, he has been pointing to his head for the past few days, perhaps indicating headache. He is US-born and frequently travels to Guyana, where he has been residing for the past 4 months with his maternal family. Treatment in Guyana included a 7-day course of amoxicillin-clavulanate for presumed acute otitis media and a subsequent course of an unknown antibiotic for treatment of pharyngitis and suspected bacteremia. Computed tomography of his head performed 1 month after onset of symptoms revealed hydrocephalus, and he returned 1 day later to the United States for further medical care.

At initial presentation he is afebrile (100°F [37.8°C]) with a heart rate of 128 beats/min, respiratory rate of 20 breaths/min, blood pressure of 121/92 mm Hg, and oxygen saturation of 97% in room air. He appears malnourished (weight of 10 kg [<2nd percentile]) and is noted to have a normal-shaped head (head circumference, 50 cm [58th percentile]). He is irritable and listless at times. Cranial nerve examination results are normal, and he moves all his extremities equally. Nuchal rigidity is not appreciated. He demonstrates nasal flaring and suprasternal and subcostal retractions, but lung auscultation was normal. The remainder of the examination findings are normal.

AUTHOR DISCLOSURE Drs Balamohan, Rubin, Assaad, and Hagmann have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

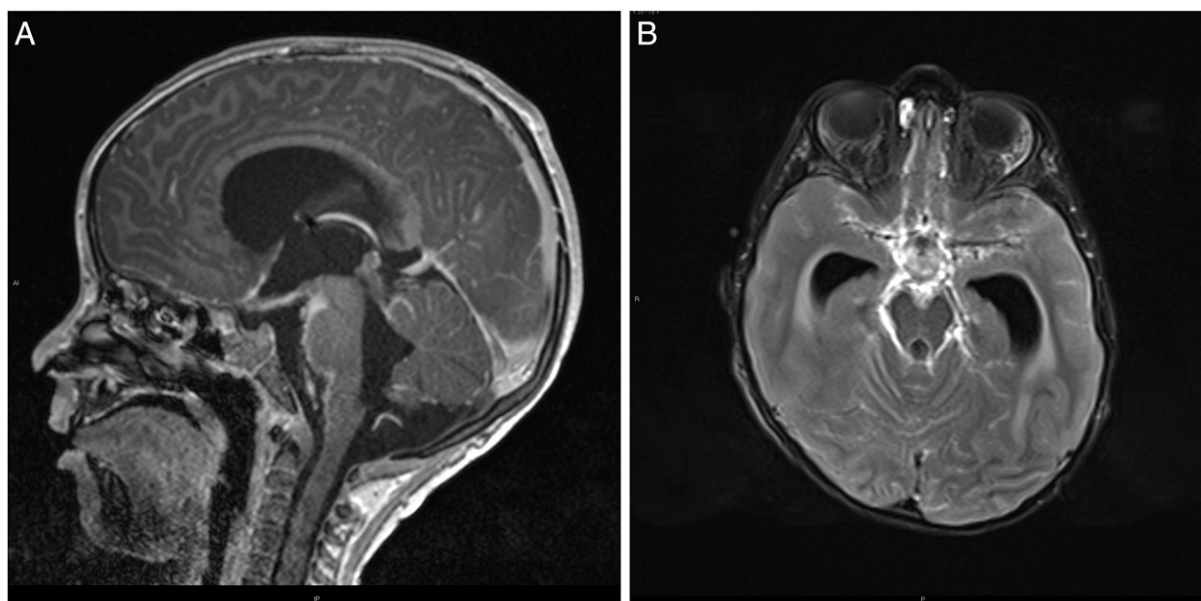


Figure 1. Magnetic resonance images of the patient's brain. A. Sagittal T1-weighted magnetization-prepared rapid gradient-echo postcontrast view demonstrating basal cistern and leptomeningeal enhancement. B. T2-weighted fluid-attenuated inversion recovery fat-saturated postcontrast view demonstrating leptomeningeal and cisternal enhancement involving the quadrigeminal and suprasellar cisterns.

Laboratory studies reveal a white blood cell count of $14,300/\mu\text{L}$ ($14.3 \times 10^9/\text{L}$), hematocrit value of 39%, platelet count of $487 \times 10^3/\mu\text{L}$ ($487 \times 10^9/\text{L}$), serum sodium level of 131 mEq/L (131 mmol/L), and normal liver transaminase levels. Magnetic resonance imaging of the head shows dilatation of the lateral, third, and fourth ventricles without evidence of aqueduct obstruction. After contrast administration, marked basilar and leptomeningeal enhancement is evident (Fig 1).

DISCUSSION

Our patient had signs of increased intracranial pressure. He was emergently intubated and underwent right frontal ventriculostomy (opening pressure of >40 cm H_2O) and externalized ventricular drain placement. His ventricular cerebrospinal fluid (CSF) had 14 nucleated cells (28% segmented cells, 56% lymphocytes, 16% monocytes), 16 red blood cells, a glucose level of 44 mg/dL (2.44 mmol/L), and a protein level of 0.03 g/dL (0.32 g/L). The CSF Gram-stain and acid-fast bacillus (AFB) stain were negative, as was cryptococcal antigen. The CSF nucleic acid amplification (NAA) assay was negative for *Escherichia coli* K1, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, cytomegalovirus, enterovirus, herpes simplex viruses 1 and 2, human herpesvirus 6, human parechovirus, varicella-zoster virus, and *Cryptococcus neoformans*. In view of his subacute presentation with basilar meningitis and substantial time

spent in a tuberculosis (TB)-endemic region, TB meningitis (TBM) was a likely diagnosis, and he was empirically started on 4-drug therapy (rifampin, isoniazid, pyrazinamide, and ethionamide), along with corticosteroid therapy. A chest radiograph was normal, and 3 sequential gastric aspirate samples tested negative for AFB by smear. Results of a TB skin test and TB interferon- γ release assay were negative. One of 2 separate CSF samples tested positive for *Mycobacterium tuberculosis* by an NAA assay. In addition, the CSF (after 17 days of incubation) and 1 of 3 sputum cultures (after 20 days of incubation) grew *M tuberculosis*, and the sensitivity testing indicated a pansensitive organism. Human immunodeficiency virus infection was ruled out. The externalized ventricular drain was converted to a ventriculoperitoneal shunt on the fourth hospital day. As the boy's appetite and energy level started to improve, he tolerated his anti-TB medication by mouth very well. After receiving a 2-week course of prednisolone (2 mg/kg daily), his corticosteroids were tapered over a 3-week period. He returned to his normal self and baseline activity level within 4 weeks of discharge. He has currently completed 4 months (of a planned 12-month course) of anti-TB therapy and remains well.

The Condition

TBM is the most debilitating and frequently fatal form of TB. (1) Although rare, occurring in less than 2% of all patients with TB, (2) it disproportionately affects young children. (1) Central nervous system TB is thought to arise from

lymphohematogenous spread of tubercle bacilli during initial infection, where they form a caseous lesion in the brain, also known as the Rich focus. Tubercle bacilli are discharged from there into the subarachnoid space, resulting in inflammation that has a predilection for the base of the brain and may result in cranial nerve III, VI, and VII involvement. A thick and gelatinous exudate forms and can interfere with normal CSF flow, resulting in communicating hydrocephalus, and can extend along vessels into the cortex and lead to infarction. (3) Hence, on neuroimaging (computed tomography or magnetic resonance imaging), hydrocephalus and basilar meningeal enhancement are most commonly encountered. (3)(4)

Clinically, 3 stages of TBM have been described. In stage I, nonspecific constitutional symptoms, headache, (2) and personality change (3) are seen. Stage II is manifested by symptoms of meningitis (nuchal rigidity, vomiting, seizures), cranial nerve abnormalities, and long tract signs. Stage III is characterized by coma, hemiplegia or paraplegia, decerebrate or decorticate posturing, progressive vital sign changes, and eventual death. (2)(4)

Diagnosis

The diagnosis of TBM is challenging and often requires a high index of suspicion in a child with a subacute presentation of meningitis, with or without hydrocephalus. During the clinical evaluation of a child with suspected TBM, alternative infectious causes of bacterial, viral, fungal, and protozoal origin, as well as noninfectious causes (eg, systemic vasculitic syndromes, hemorrhage, or leukemic infiltrates) need to be considered as possible differential diagnoses. In this context, the review of the epidemiologic history is crucial to identify patients who have either traveled to TB-endemic regions or been exposed to ill contacts with TB.

Analysis of CSF usually demonstrates lymphocytic predominant pleocytosis, hypoglycorrhea, and an elevated protein level. However, ventricular CSF may be normal or show only subtle evidence of inflammation compared with lumbar CSF. (3) Tuberculin skin testing results are frequently non-reactive (>45% of cases). (3)(4) The diagnostic modality of choice is microbiological confirmation, although this can be challenging. Staining with AFB and mycobacterial culture of CSF is positive in less than 10% and approximately 35% of patients, respectively. (5) The yield can be increased if a large volume of CSF (≥ 10 mL) is cultured. NAA testing of CSF, although an off-label use of the test, may be helpful in establishing the diagnosis. A positive result can be used as

evidence of TBM because a false-positive result is unlikely. However, false-negative results are common, and a negative result does not exclude TBM. (6)

Management

TBM has the greatest morbidity and mortality rates of all *M tuberculosis* infections, with the rates directly correlated to the stage at which effective therapy is initiated. (4) Therefore, children with clinical, laboratory, or radiologic findings suspicious of TBM and the presence of epidemiologic risk factors should be empirically started on anti-TB treatment. Treatment for TBM consists of 4 drugs initially (rifampin, isoniazid, pyrazinamide, and ethionamide or streptomycin); ethionamide is preferred over ethambutol due to its increased blood-brain barrier penetration. (1) Treatment with pyrazinamide and ethionamide is usually stopped after 2 months (provided drug resistance has been ruled out by susceptibility testing), and isoniazid and rifampin are continued for 9 to 12 months. Corticosteroids (eg, 1–2 mg/kg per day of prednisone) for the first month of treatment followed by a taper has been associated with a reduced risk of mortality (7)(8) and improved intellectual outcome. (8) Ventriculoperitoneal shunt placement is often warranted to relieve intracranial pressure, prevent herniation, and improve neurologic deficits. (3)(4)

Lessons for the Clinician

- In tuberculosis (TB) low-endemicity regions such as the United States, travel and exposure history are key to considering the diagnosis of TB in a child.
- The symptoms of TB meningitis (TBM) are often initially subtle and develop subacutely; hence, a high index of suspicion is required.
- Cranial computed tomography and, in particular, magnetic resonance imaging may increase suspicion of TBM by demonstration of basilar enhancement with noncommunicating hydrocephalus.
- The diagnostic modality of choice is microbiological confirmation of mycobacterial infection from cerebrospinal fluid. The diagnostic yield can be improved by obtaining high-volume cerebrospinal fluid samples (≥ 10 mL) and using nucleic acid amplification-based tests.
- Therapy for TBM consisting of a 4-drug regimen and corticosteroids should be started empirically due to the high degree of mortality and morbidity while the diagnosis is being confirmed.

References for this article are at <http://pedsinreview.aappublications.org/content/40/4/191>.

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Case 1: Intermittent Fevers, Persistent Vomiting, and Lethargy in a 3-year-old Boy

Archana Balamohan, Lorry G. Rubin, Peter Assaad and Stefan H.F. Hagmann

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1 New-Onset Seizures in a 16-year-old Girl Recently Emigrated from Africa

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EDITOR'S NOTE

AUTHOR DISCLOSURE Drs Cafferty, Howard, and Kaila have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

After Match Day this month, some senior medical students will be heading off for global health rotations. Some residents and practicing physicians are finalizing plans for summer service-learning trips in countries far from home. Meanwhile, pediatric offices in North America are increasingly seeing recent immigrants who might carry conditions that seem uncommon. To help prepare all readers in all parts of the world, *Index of Suspicion* highlights cases this month that are particularly relevant to readers interested in global health.

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

A 16-year-old previously healthy girl with recent international emigration with refugee status from Tanzania presents via emergency medical services (EMS) with new-onset seizurelike activity. She had spent the 48 hours immediately before presentation traveling from Tanzania to the United States via Switzerland, with minimal sleep. The EMS was called to the home after the family found the girl lying on the floor covered in vomit with shaking movements of her extremities and eyes rolled back. She is without seizure activity and is not postictal in appearance when EMS arrives. She is noted to have a history of malaria several years earlier (treated and without recurrence), but no other medical problems. She has no personal or family history of seizure disorders, she is not taking medications, and there is no concern for illicit substance abuse, medication ingestion, or precipitating trauma. She has had no recent fever, headache, abdominal pain, vomiting, diarrhea, or other concerns.

During transport to the emergency department (ED) she receives a dose of ondansetron. On arrival, her temperature is 98.4°F (36.9°C), respirations are 16 breaths/min, heart rate is 87 beats/min, blood pressure is 133/84 mm Hg, and oxygen saturation is 100% on room air. Physical examination reveals no distress. Her head is normocephalic and atraumatic. Her neck is supple without meningismus. Her chest is clear to auscultation, with normal heart sounds. Her abdomen is nondistended, nontender, and without organomegaly. Her skin is clear, without rash or petechiae. Results of a complete neurologic examination are



Figure 1. Computed tomographic scan of the head without contrast. There is a 0.7-cm benign-appearing right occipital lobe calcification without associated mass effect.

normal, her Glasgow Coma Scale score is 15, and her glucose level is 120 mg/dL (6.7 mmol/L). The values for complete blood cell count (with differential count), serum electrolytes, blood urea nitrogen, creatinine, liver enzymes, and lipase are within normal limits. A computed tomographic (CT) scan of the head without contrast reveals a 0.7-cm benign-appearing right occipital lobe calcification without associated mass effect of uncertain etiology and significance (Fig 1). After imaging, the girl begins to actively seize, with generalized tonic-clonic activity and an episode of urinary incontinence. She receives 1 mg of lorazepam intravenously, oxygen via a nonrebreather mask, and, subsequently, a loading dose of levetiracetam due to ongoing seizure activity. During hospitalization, routine electroencephalography is performed and the results are normal during a state of wakefulness. Magnetic resonance imaging (MRI) of the brain and entire spine with and without contrast reveals the diagnosis.

DISCUSSION

Differential Diagnosis

The differential diagnosis for this adolescent's presentation includes neurocysticercosis, central nervous system (CNS) toxoplasmosis, CNS cryptococcosis, tuberculosis meningitis or CNS tuberculosis, cerebral amebiasis, neurosarcoidosis, healed brain abscess, CNS tumors, healed infarct or hematoma, or benign calcifications with unexplained seizure etiology.

Actual Diagnosis

Magnetic resonance imaging of the brain and entire spine with and without contrast was performed during this

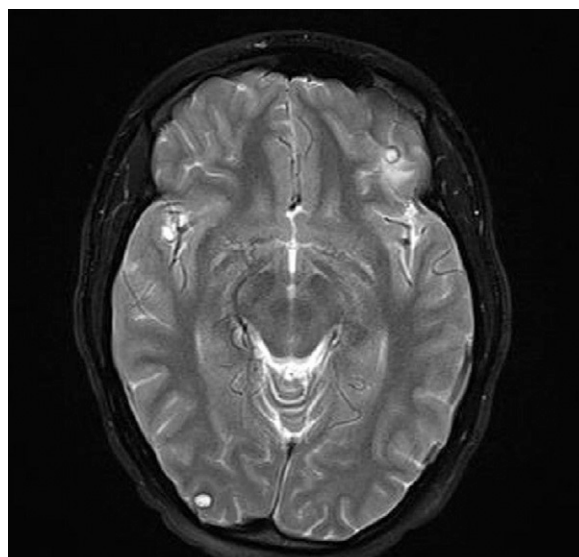


Figure 2. Magnetic resonance imaging of the brain with contrast. There is a 5-mm peripherally enhancing lesion with surrounding vasogenic edema in the left inferolateral frontal lobe, likely representing a colloidal vesicular neurocysticercosis lesion. An additional nonenhancing lesion with similar signal characteristics in the right occipital lobe is present, matching the area of calcification on a previous computed tomographic scan.

hospitalization, which was significant for a 5-mm peripherally enhancing lesion with surrounding vasogenic edema in the left inferior lateral frontal lobe, consistent with a colloidal vesicular neurocysticercosis lesion (Fig 2). An additional nonenhancing lesion in the right occipital lobe was correlated with the area of calcification on previous CT. No abnormal signal was present in the spinal cord.

Patient Course

Throughout hospitalization the patient was continued on maintenance levetiracetam therapy. A dilated ophthalmologic examination was performed, which was negative for ophthalmic cysticercosis. Cysticercosis serology and stool ova and parasites examination sent to the Centers for Disease Control and Prevention (CDC) were negative. Due to concern for neurocysticercosis despite negative serologic testing (1) the patient was treated with cysticidal therapy (albendazole) with concomitant corticosteroids. She did not receive combination therapy with praziquantel given that her disease was not multicystic in nature. The patient continues on maintenance antiepileptic medications and has remained seizure-free.

The Condition

Taenia solium produces an intestinal infection caused by adult tapeworms that occurs after ingestion of contaminated

pork. (2) The presence of *T solium* cysts in the brain is termed *neurocysticercosis*, the most serious form of the disease. Seizures are the most common manifestation of neurocysticercosis, present in 70% to 90% of symptomatic patients. (1) In endemic regions, neurocysticercosis is regarded as the “great imitator,” with the ability to mimic nearly all neurologic disorders. (3) Confusion, poor attention, balance difficulties, hydrocephalus, chronic meningitis, cranial nerve abnormalities, and stroke are rare but may occur. Symptoms depend on the number, location, size, and stage (viable, degenerating, or calcified) of cysticerci. Live cysts do not incite a major inflammatory reaction; cyst degeneration releases parasite antigens and may result in an acute inflammatory response with significant morbidity. Necrotic larvae may resorb or calcify and produce local scarring, which serves as a focus for seizure activity. (1)

The World Health Organization recently named *T solium* the “food-borne parasite of greatest global concern.” (4) Infection rates of cysticercosis (including neurocysticercosis) are highest in developing countries with free-roaming pigs and poor sanitation throughout Latin America, Asia, and Africa. (1) Neurocysticercosis is the most frequent preventable cause of epilepsy in developing nations, accounting for an estimated 30% of cases where the parasite is endemic. (5) Although *T solium* infection is not endemic in the United States and local transmission is low, increases in immigration from endemic regions has led to a higher incidence of neurocysticercosis locally. (3) Of patients presenting to an ED in the United States with seizures, 2% to 10% are ultimately diagnosed as having neurocysticercosis. (6)

Neurocysticercosis is challenging to diagnose, particularly in resource-limited countries worldwide, where CT and MRI are not readily available. Diagnosis of neurocysticercosis usually requires CT or MRI, as well as serologic testing (by enzyme-linked immunoelectrotransfer blot [EITB] or commercial enzyme-linked immunoassays). The EITB is highly sensitive (94% sensitivity) in cases of neurocysticercosis in which 2 or more lesions are present. (7) However, EITB has low sensitivity (28%) in cases of single lesion disease or calcified cysts. (7) In cases of clinically suspected and MRI-proven neurocysticercosis, anticysticercus antibodies may be positive in less than 50% of patients. (8) Imaging of the CNS demonstrates a contrast-enhancing ring around a cyst due to local inflammation and resultant edema. A single enhancing nodule is more commonly found in individuals younger than 30 years, and inflammation is more exaggerated in children. (3)

Treatment/Management

Treatment of neurocysticercosis consists of anticonvulsant therapy (if indicated), corticosteroids, antihelminthic treatment, and, at times, neurosurgical intervention. The 2017 Infectious Diseases Society of America and American Society of Tropical Medicine and Hygiene guidelines on the diagnosis and treatment of neurocysticercosis recommend albendazole monotherapy (15 mg/kg per day divided into 2 daily doses) for 10 to 14 days in patients with 1 to 2 viable parenchymal cysticerci. (9) Combination therapy with both albendazole and praziquantel for the treatment of multicystic intraparenchymal neurocysticercosis has demonstrated superior results without increased adverse effects. (10) Caution must be taken when initiating antihelminthic treatment because larval death provokes an inflammatory response that may result in increased symptoms acutely. As a result, co-administration of corticosteroids that cross the blood-brain barrier (eg, dexamethasone) is usually indicated. Antihelminthic treatment is not beneficial in cases of calcified cysts (dead parasite).

Recurrence of seizures after initiation of treatment occurs at a rate of 10% to 34% in patients with calcified lesions, 13% to 48% in individuals with a single granuloma, and 54% in those with multicystic disease. (3) However, many individuals tolerate weaning off of anticonvulsant therapy after antihelminthic treatment is complete.

CONCLUSION

Neurocysticercosis, the leading cause of epilepsy worldwide, is endemic in many of the countries worldwide from which individuals emigrate to the United States, resulting in an increase of cases locally. (6) Live cysts in the brain are often asymptomatic, but cyst degeneration releases parasite antigens and incites an acute inflammatory response, which can provoke neurologic sequelae. Before international travel, CDC guidelines state that US-bound refugees should be treated with a single dose of albendazole and praziquantel for the treatment of presumed parasite infection. Predeparture treatment was confirmed for our patient, which likely initiated the cysticidal activity in the brain resulting in inflammation and edema and provoking first-time seizures. Although aimed at treatment of intestinal parasitic disease, knowing that provocation of neurologic symptoms may result after predeparture treatment should raise awareness in all providers that new-onset seizures occurring in immigrant refugee populations shortly after arrival in the United States are highly suspicious for neurocysticercosis.

Lessons for the Clinician

- Neurocysticercosis, the leading cause of epilepsy worldwide, is now more commonly seen in the United States as individuals emigrate from areas in which *Taenia solium* is endemic.
- Neurocysticercosis is difficult to diagnose and requires a high clinical suspicion. Enzyme-linked immunoelectro-transfer blot is highly sensitive for cases in which 2 or more central nervous system lesions are present but has low sensitivity in cases of single-lesion disease or calcified cysts.
- Live cysts are often asymptomatic. Cyst degeneration incites a local acute inflammatory response, which can provoke seizures.
- Predeparture treatment, as recommended by the CDC for the treatment of intestinal parasitic disease, may initiate

cysticidal activity in the central nervous system, resulting in neurologic sequelae.

- Albendazole monotherapy is recommended for patients with 1 to 2 viable parenchymal cysticerci. Combination therapy with albendazole and praziquantel has been shown to be beneficial for multicystic intraparenchymal neurocysticercosis. Co-administration of corticosteroids with antihelminthic medication counters the host inflammatory response that occurs with larval death and is beneficial in decreasing the occurrence of seizures when starting therapy.

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Case 1: New-Onset Seizures in a 16-year-old Girl Recently Emigrated from Africa

Rachel Cafferty, Cynthia Howard and Rahul Kaila

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1 Syncope in a 16-year-old Girl

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EDITOR'S NOTE

We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: <https://mc.manuscriptcentral.com/pir>.

AUTHOR DISCLOSURE Drs Sadanand, Ladell, and Fischer have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy 16-year-old girl is transferred from a referring facility for syncope and altered mental status. The previous day, she received the meningococcal vaccine. After a stressful conversation with her father, she began to complain of chest pain, diaphoresis, and nausea. She vomited, became clammy, and fell to the ground unresponsive. She was brought to the referring facility, where she was given epinephrine, diphenhydramine, methylprednisolone, famotidine, and 4 L of isotonic fluids for a possible anaphylactic reaction to the vaccine. She remained groggy, tachycardic, and anuric.

After transfer, her vital signs are as follows: temperature, 97.5°F (36.4°C); heart rate, 120 beats/min; respiratory rate, 23 breaths/min; blood pressure, 95/44 mm Hg; and oxygen saturation, 98% on room air. On physical examination, she is sleepy but responsive, with a Glasgow Coma Scale score of 15, delayed capillary refill, 2+ pulses, and hepatomegaly to 4 cm below the costal margin. The remainder of her examination findings are within normal limits.

She denies pain, fevers, night sweats, unintended weight loss, exercise intolerance, or peripheral edema. She reports a similar episode during final exams during her previous school semester that was attributed to stress after a reassuring evaluation. She was started on an antidepressant medication, which she discontinued taking 3 weeks ago due to improvement in symptoms.

Initial laboratory results show metabolic acidosis with venous pH 7.29; carbon dioxide level, 38 mEq/L (38 mmol/L); white blood cell count, 28,800/ μ L (28.8×10^9 /L); lactate level, 40.5 mg/dL (4.5 mmol/L); blood glucose level, 187 mg/dL (10.4 mmol/L); troponin I level, 0.04 ng/mL (0.04 μ g/L); brain-type natriuretic peptide level, 42 pg/mL (42 ng/L); and cortisol level, 49 μ g/dL (1,352 nmol/L). Chest radiography shows diffuse nodular opacities throughout both lungs (Fig 1). An electrocardiogram is performed that shows right axis deviation and pericardial inflammation (Fig 2).

She is hospitalized in the ICU due to hypotension and tachycardia and is initiated on a vasopressor drip to maintain blood pressures. An echocardiogram leads to the cause of her syncope.

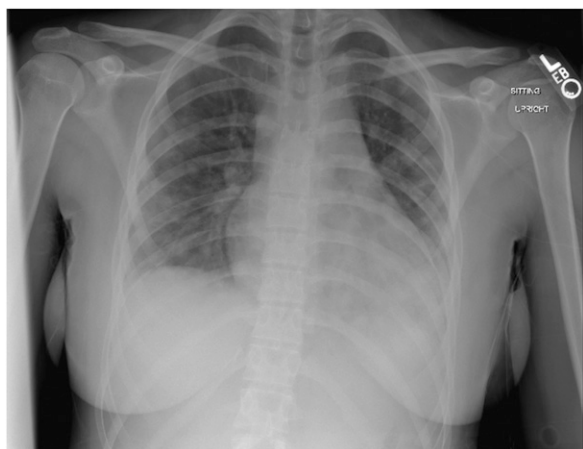


Figure 1. Patient's chest radiograph.

DISCUSSION

Differential Diagnosis

Our initial differential diagnoses included infectious myocarditis, dilated cardiomyopathy, bacterial sepsis, pulmonary embolism, ingestion, atrial myxoma, lymphoma, tuberculosis, hemophagocytic lymphohistiocytosis, human immunodeficiency virus, and fungal pneumonia.

Actual Diagnosis

Echocardiography showed a right atrial mass extending into the superior vena cava and a large pericardial effusion with

tamponade physiology. A chest computed tomographic (CT) scan showed a mass centered in the epicardium of the right atrial wall involving the pericardium and extending through the myocardium to fill the right atrium (Figs 3 and 4). It also showed a small right pleural effusion, a heterogeneous appearance of the liver, small-volume ascites, and numerous small masses in the lung fields. The right atrial mass was biopsied, and a sample was sent to the pathology laboratory. Microscopic features, immunohistochemistry panel results, and clinical location of the mass in the right atrium were most consistent with a primary cardiac angiosarcoma with pulmonary metastases.

The Condition

A recent population study found the incidence rate of primary cardiac tumors to be 1.38 per 100,000 persons per year. (1) A pediatric review at 1 center found that approximately 95% of primary cardiac tumors were benign and 5% were malignant. (2) Of these malignant tumors, primary sarcomas are more common than primary lymphomas, and cardiac angiosarcomas are the most common of the cardiac sarcomas. There is a male:female predominance of approximately 2:1 to 3:1. (3) Risk factors for angiosarcomas include previous irradiation, chronic lymphedema, exogenous toxins, and familial syndromes, including NF-1, BRCA1, BRCA2, Maffucci syndrome, and Klippel-Trenaunay syndrome. (4)

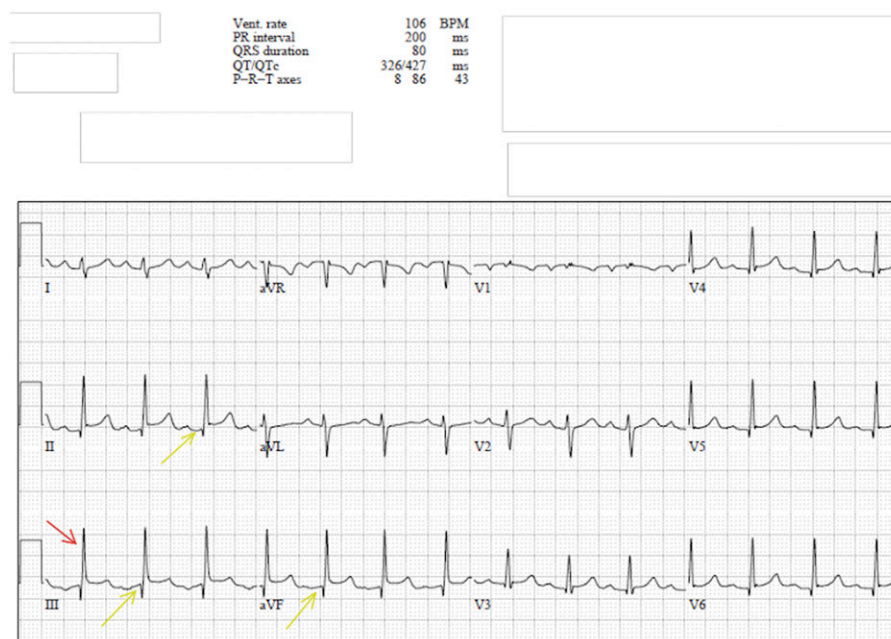


Figure 2. Patient's electrocardiogram; yellow arrows indicate PR depression showing pericardial inflammation/pericarditis, and red arrow shows right axis deviation concerning for right heart strain.



Figure 3. Patient's chest computed tomographic scan, coronal view; red arrows indicate the primary tumor.

Cardiac angiosarcomas arise from the endothelial lining of blood vessels or the lymphatic system and tend to occur in the right atrium. (3)(5) Unlike most sarcomas, they are more likely to metastasize to the liver and lungs. Unfortunately, many cardiac angiosarcomas present with these systemic metastases, which decreases the median chance of survival. (6) Treatment is generally composed of resection if possible, and chemotherapy with adjuvant radiotherapy. Cardiac angiosarcomas have low median survival times ranging from 6 to 24 months. (7) Some centers have performed orthotopic heart transplant (8) with postoperative chemotherapy; however, this has not been shown to change long-term outcomes. Future directions for treatment include immunologic therapies and autotransplant. (9)

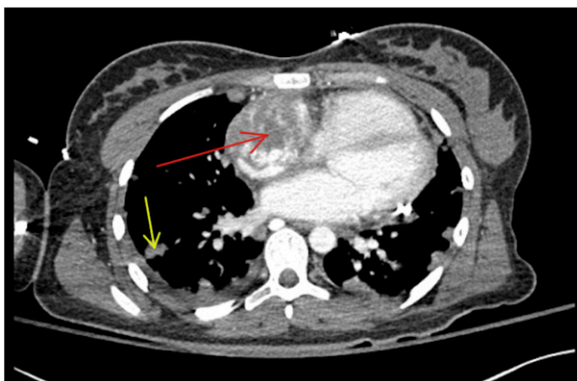


Figure 4. Patient's chest computed tomographic scan, axial view; red arrow indicates the primary tumor, and yellow arrow indicates lung metastases.

Treatment/Management

Surgical resection (if complete resection is possible), (10) chemotherapy (paclitaxel and neoadjuvant agents), radiotherapy, and palliative care consultation are advised.

Patient Course

The patient immediately underwent pericardiocentesis and was slowly weaned off vasopressors. She underwent cardiac catheterization with biopsy, and once the diagnosis was confirmed, she was started on emergent stereotactic body radiotherapy directed toward the right atrium and single-agent paclitaxel.

She recently completed stereotactic body radiotherapy divided into 5 fractions and 12 weeks of chemotherapy with paclitaxel. Her week 7 CT scan showed interval resolution in most of her pulmonary metastases and a decrease in primary tumor size by approximately 1 cm in every dimension. However, her latest CT scan, after paclitaxel therapy, shows progression of some of her remaining pulmonary lesions and several new lesions. Primary cardiac tumor size was stable on this scan. Resection of the primary tumor is not being pursued at this time due to active metastatic disease. She will likely receive more radiotherapy and recently began immunomodulatory therapy with an anti-PD1 monoclonal antibody (nivolumab) and an anti-CTLA-4 antibody (ipilimumab).

Lessons for the Clinician

- In a pediatric population, vasovagal syncope and orthostatic hypotension are more common than cardiac causes of syncope. Cardiac (electrical and structural) causes of syncope are rare (11) but can be life-threatening.
- Primary cardiac tumors can cause obstruction of circulation or poor venous return depending on location, resulting in symptoms of right heart failure.
- Because malignant primary cardiac tumors are likely to have metastases on presentation, complete imaging is important for complete diagnosis.
- Surgical resection is often the treatment of choice if malignant primary cardiac tumors can be resected completely; however, some patients still develop recurrent disease (12)(13)(14) and may benefit from adjuvant chemotherapy and radiotherapy. (15)

References for this article are at <http://pedsinreview.aappublications.org/content/40/1/37>.

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Case 1: Syncope in a 16-year-old Girl
Arhanti Sadanand, Meagan Ladell and Kayleigh Fischer
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1 An 11-year-old Girl with Depression and Electrolyte Disturbance

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EDITOR'S NOTE

On June 3, 2017, 27-year-old Alex Honnold climbed the 2,900-foot rock face of El Capitan in Yosemite National Park, alone and with neither rope nor safety net. The story is shown in the 2018 documentary film *Free Solo* and described in the 2018 book *The Impossible Climb* by Mark Synnott.

Many reading this issue of *Pediatrics in Review* have moved to new levels of responsibility this summer and might feel like they are free-soloing too.

Honnold did not do his free-solo climb on a whim. He prepared meticulously. He worked with colleagues and practiced moves for years, with ropes, on the same route that he would one day conquer on his own, unsupported. Just as with pediatric training, expertise comes with training, time, and practice.

But, what did Honnold do during the afternoon of June 3, 2017, following what the *New York Times* called “one of the great athletic feats of any kind, ever”? He worked out to strengthen his grip for future climbs. In the same way, we who care for children keep working out. We keep honing our skills. We meticulously study possible “routes” as we consider cases and differential diagnoses and management plans. After each patient care success, we keep “working out” for the next challenge.

Even so, may you use this month's *Index of Suspicion* cases to “strengthen your grip” so you can be effectively prepared to work through steep diagnostic challenges as you reach new heights of pediatric practice.

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

AUTHOR DISCLOSURE Drs Assaf, Levine, Cheung, Tamrazi, Cotter, Bryant, and Kiehna have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An 11-year-old girl with a 2-year history of major depressive disorder presents to the emergency department with 10 days of anorexia, irritability, and depressed mood. She was first diagnosed as having depression 2 years ago during a 2-month-long hospitalization that mandated a psychiatric hold for physical

aggression and suicidal ideation with concurrent anorexia requiring nasogastric feeding. Aripiprazole 1 mg daily was prescribed to target symptoms of agitation. After discharge from her first hospitalization, the patient was followed monthly by a psychiatrist and weekly by a psychotherapist, with discontinuation of pharmacotherapy 4 months later given improvement in labile mood.

Then, 11 months after that point, she was noted to clinically deteriorate, with development of severe apathy, irritability, oppositionality, and anorexia despite the absence of identifiable stressors. She was admitted again, this time for 2 weeks, for treatment of depression, oral aversion, and anorexia. Aripiprazole therapy was briefly reinitiated, but the patient was thought to have medication-induced dystonia (fist-clenching) and syndrome of inappropriate antidiuretic hormone, with a serum sodium level of 118 mEq/L (118 mmol/L). Sodium values returned to normal levels after water restriction, oral sodium supplementation, and discontinuation of aripiprazole. Concurrent diffuse headaches were evaluated with a contrast computed tomographic scan of the head, which did not demonstrate any structural abnormality or calcification. On discharge, mood and behavior were improved on fluoxetine 10 mg nightly. However, after approximately 6 weeks, the patient's depression, irritability, aggression, and oral intake worsened, and she is seen in our emergency department for these symptoms, meeting the criteria for inpatient psychiatric hospitalization.

The patient measures 51.6 in (131 cm) in height (less than the third percentile, z score = -2) and weighs 65 lb (29.3 kg) (eighth percentile, z score = -1.39), with a BMI of 18.85 (67th percentile, z score = 0.5), growth velocity of 1.0 in (2.5 cm) per year, and midparental height of 61.5 in (156.25 cm). Although she demonstrated a poor growth trajectory, the patient had limited follow-up with her primary pediatrician, and no previous endocrinologic evaluation had been completed. Vital signs on presentation are within normal limits, and the physical examination reveals a Tanner stage I prepubertal female (pubic hair I, breasts I) with no neurologic deficit. She is seen by a psychiatry consultant in the emergency department and is diagnosed as having major depressive disorder recurrent episode with atypical features, including increased sleep.

She is admitted to the hospital for close observation and is started on mirtazapine to target depression and poor oral intake. She develops asymptomatic hypoglycemia (glucose level of 52 mg/dL [2.9 mmol/L]) and hyponatremia (sodium level of 125 mEq/L [125 mmol/L]). Her morning cortisol level is low (<1 μ g/dL [<27.6 nmol/L]), with an inappropriately normal corticotropin level (9 pg/mL [2 pmol/L]) and a subsequent failed corticotropin stimulation test, with a peak cortisol level of 2.7 μ g/dL (74.5 nmol/L). Additional endocrine evaluation reveals

a low free thyroxine level (0.68 ng/dL [8.75 pmol/L]), with an inappropriately normal thyrotropin level (1.41 mIU/L), a low insulinlike growth factor I level (45 ng/mL [5.9 nmol/L], -3.4 SD), and prepubertal gonadotropin and estradiol levels. Further evaluation reveals the etiology of her condition.

DISCUSSION

Gadolinium-enhanced magnetic resonance imaging (MRI) of the brain is performed, demonstrating a cystic mass in the sella measuring $1.4 \times 1.4 \times 2.1$ cm with suprasellar extension, displacing the optic chiasm superiorly (Fig, top row). Cyst contents are hyperintense on T1-weighted MRI and predominantly hypointense on T2-weighted MRI, with hemosiderin staining on the gradient recalled echo sequence suggestive of previous hemorrhage. Given the new findings on MRI, an underlying sellar mass supports the reason for the endocrinologic disturbances recently discovered in this patient. A differential diagnosis includes a hemorrhagic Rathke cleft cyst (RCC), predominantly cystic craniopharyngioma, hemorrhagic macroadenoma, and a germ cell tumor.

The Disorder

Central endocrinopathy is frequently associated with sellar masses, and given the patient's indolent symptoms and MRI findings, an RCC was suspected. Both RCC and adamantinomatous craniopharyngioma (ACP) originate from ectopic remnants of the Rathke pouch formed during embryonic development of the pituitary gland and have similar clinical manifestations. (1) An ACP is more likely to have calcifications on imaging, which were absent in this case. (2) On pathologic examination, an ACP typically contains squamous epithelium, whereas an RCC characteristically contains well-differentiated columnar epithelium and cilia, although the 2 conditions have been reported to coexist given their common embryologic origin. (3) In this patient, serum and cerebrospinal fluid α -fetoprotein and β -human chorionic gonadotropin test results were both negative, making germ cell tumor unlikely.

Most RCCs are asymptomatic, with the incidence ranging from 3% to 22% in adult autopsy studies. (4) Although only 10% of RCCs are found in patients younger than 16 years, these are usually symptomatic, prompting brain imaging. (5) When RCC enlargement causes acute or subacute symptoms, it commonly manifests over a period of weeks to years with headache (70%–85% of patients), visual impairment (33%), and endocrine dysfunction (66%), with diabetes insipidus, precocious puberty, and growth delay the most frequently encountered endocrinopathies. (5)

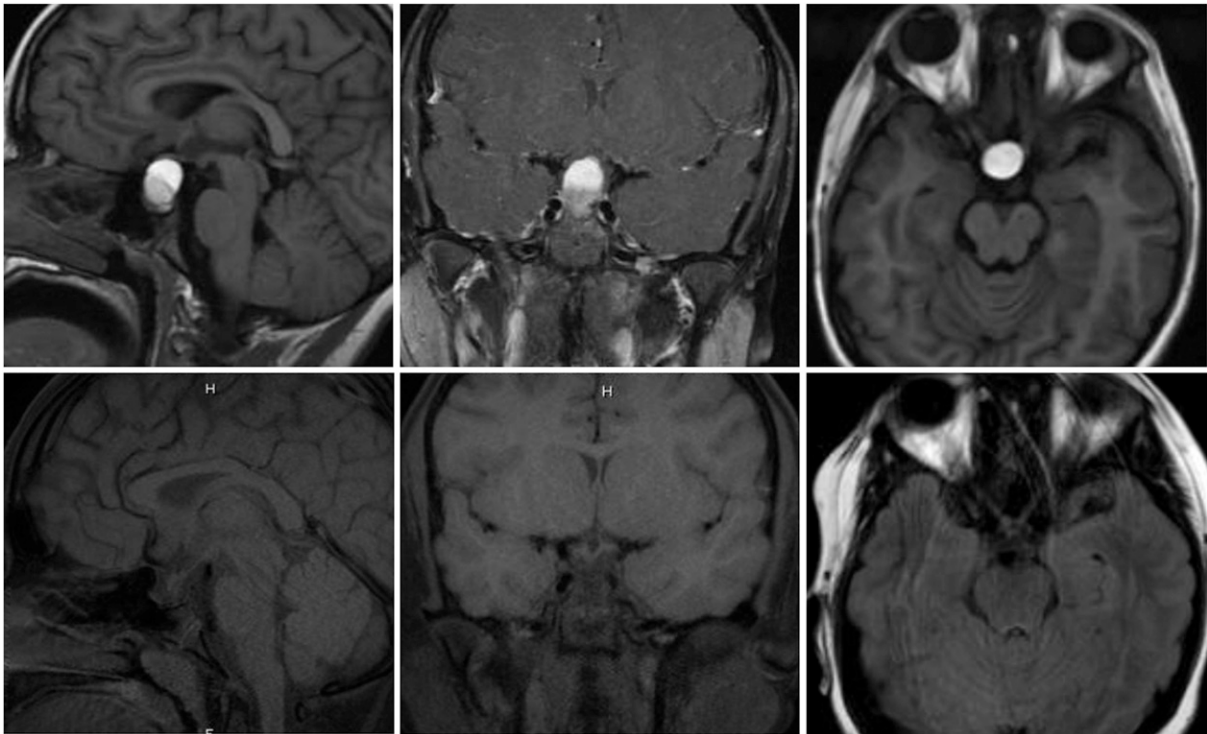


Figure. Comparison of preoperative T1-weighted magnetic resonance images (MRIs) (upper row) and MRI with dedicated images of the sella 18 months after resection via the transsphenoidal approach (bottom row). The hyperintense cystic lesion originally measured $1.4 \times 1.4 \times 2.1$ cm, with displacement of the optic chiasm superiorly. No residual cyst is evident in the postoperative images.

Intracystic hemorrhage or inflammation secondary to cyst contents is possible and may lead to a more severe acute presentation. (5)

Diagnosis and Treatment

Clues to an underlying central endocrinopathy early in our patient's hospital admission included headache and vomiting in an 11-year-old prepubertal female patient whose height measured less than the third percentile for age, with concurrent and persistent hyponatremia (sodium level of 125–130 mEq/L (125–130 mmol/L)). These findings together ultimately prompted an evaluation of a morning cortisol level and further endocrinologic evaluation, which revealed evidence of relatively low corticotropin, thyrotropin, and growth hormone levels. Bone age was found to be concordant with chronological age. An ophthalmologic examination revealed bitemporal superior quadrantanopsia and normal visual acuity, consistent with inferior chiasmal compression.

Although behavioral disturbance and executive dysfunction are well-documented consequences of hypopituitarism and in particular hypocortisolism, an association specifically between RCC and psychiatric manifestation is less described in the literature. (6) To begin with, the true incidence of pituitary cysts in childhood is not known but

is thought to be uncommon, with asymptomatic lesions incidentally found in 4 of 341 children (1.2%) younger than 15 years in a 10-year single-center retrospective review of brain MRIs. (7) According to national mental health surveillance data for 2005 to 2011 from the Centers for Disease Control and Prevention (CDC), the prevalence of depression in children aged 3 to 17 years was reported to be 2.1%. (8) A delay in the diagnosis in our case may be attributed to the slow growth of RCC and the indolent course of additional somatic symptoms other than headache as well as limited access to primary pediatric and endocrine specialty care during the 2 years between the diagnoses of mood disorder and pituitary mass. Panhypopituitarism at the time of presentation of an RCC has been reported in up to 25% of adult patients (4) but is less frequently reported in children. (9) Note that during the 2 years before discovery of the RCC, our patient's psychiatric and somatic symptoms were not controlled with antidepressant medications.

Asymptomatic patients with incidental discovery of a small cystic lesion can be observed. (1) For patients with progressive enlargement of their lesion, endocrinopathies, or visual disturbances, surgical intervention is warranted, with pathologic slides helping differentiate RCCs and ACPs. Most sellar/suprasellar tumors are approached via the

transsphenoidal route. The most common surgical strategy includes fenestration of the cyst, evacuation of cyst contents, and biopsy of the cyst wall. (1) Generally, there is minimal attempt to remove the cyst wall, and the sellar floor is left open to allow cyst drainage into the sphenoid sinus. This strategy relieves symptoms and has minimal associated pituitary dysfunction but has been associated with higher recurrence rates, approaching 30% in some series. (4) Complete resection is associated with lower recurrence rates, but there is a higher risk of pituitary dysfunction and cerebrospinal fluid leak. (1)

The patient was prescribed physiologic dosing of hydrocortisone (10 mg/m² per day) for secondary adrenal insufficiency, levothyroxine for central hypothyroidism, and desmopressin for central diabetes insipidus. Cyst removal was performed via the endoscopic endonasal transsphenoidal approach. On microscopic examination, intact fragments of cyst epithelium were composed of tall columnar cells with well-preserved apical cilia, a histologic finding consistent with RCC. (10) No foci of “wet keratin,” stellate reticulum, or stratified squamous epithelium were present in the specimen, and, therefore, an ACP was much less likely. Repeated ophthalmologic testing with a Humphrey visual field study 3 months postoperatively reveals resolution of bitemporal superior quadrantanopsia. No residual cyst is detected on repeated MRI 5 and 18 months after neurosurgery (Fig, bottom row). Now nearly 13 years old and more than 18 months from the operative date, the patient has sustained resolution of headaches, improved energy and appetite, with normal mood and behavior off psychotropic

medications. She requires ongoing replacement of hormones given central endocrinologic dysfunction and is maintained on hydrocortisone, levothyroxine, growth hormone, and desmopressin, with planned initiation of estradiol supplementation given inadequate pubertal growth secondary to hypogonadotropic hypogonadism.

Lessons for the Clinician

- Diligently following growth trajectory and Tanner staging for even subtle abnormalities may be critical in promptly diagnosing an underlying endocrinopathy, especially in the setting of unexplained electrolyte disturbance
- Only a minority of Rathke cleft cysts (RCCs) present in children; however, they are more likely to be symptomatic, in contrast to adults.
- The most common presenting symptoms of RCC include headache, visual disturbances, and endocrine dysfunction.
- Craniopharyngiomas manifest similarly to RCCs, and although each has characteristic radiologic findings, histopathologic analysis is needed to distinguish one from the other.
- Evacuation of cyst contents is the most common surgical approach, and cysts rarely recur. Complete cyst resection carries a higher risk of pituitary dysfunction and cerebrospinal fluid leak.

References for this article are at <http://pedsinreview.aappublications.org/content/40/8/421>.

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Case 1: An 11-year-old Girl with Depression and Electrolyte Disturbance
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1 Progressive Weakness in a Previously Healthy 4-year-old Boy

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EDITOR'S NOTE

Ahh, summertime! Some of us look forward to vacations, perhaps reading on a beach or in a quiet forest. We like summer as we share stories with friends, make new memories, and broaden horizons. Of course, you can take *Pediatrics in Review* along on your summer vacations! You can enjoy the “stories” of *Index of Suspicion* cases, and you can make new memories as you learn of new diagnoses and treatments. You can broaden the scope of your care of future patients. You might even see a patient later this summer who has one of the diagnoses featured in this month's issue. Enjoy!

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

A previously healthy 4-year-old boy is carried into the emergency department with progressive weakness affecting all 4 extremities for a 24-hour duration. For the past 2 days, the boy has been more fatigued and complaining of right knee and lower back pain. The parents report no history of trauma. He has a normal appetite, without nausea, vomiting, or recent gastrointestinal illness. He has no dysuria, polyuria or incontinence, chest pain, or cough.

On examination he is afebrile, with normal vital signs. He is mildly distressed, without toxic appearance. There are no obvious rashes, abrasions, ecchymoses, or other findings on exposed skin areas. He is alert and oriented to person, place, and time. On cranial nerve examination his pupils are reactive bilaterally, and extraocular movements are intact. However, slowed smooth pursuit and horizontal nystagmus are observed. Bilateral facial droop is present, along with 4/5 strength of the sternocleidomastoid muscles. He is experiencing diffuse hypotonia, with no spontaneous movement of the bilateral lower extremities. He has 2/5 strength in the distal upper extremities bilaterally. Deep tendon reflexes are absent. He has intact sensorium throughout. Examination of the joints reveals

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normal passive range of motion. All other physical examination findings are normal.

DISCUSSION

After a thorough examination of the skin, an engorged tick was detected on the scalp and was properly and fully removed. Findings on laboratory evaluation were normal, including a complete blood cell count, C-reactive protein level, complete metabolic panel, and erythrocyte sedimentation rate. The boy was admitted to the hospital. Within 8 hours of tick removal he was sitting unsupported, and by 12 hours he was ambulating without assistance.

Differential Diagnosis

Acute-onset paralysis in children has a broad differential diagnosis, and it is important to establish whether the paralysis is due to an upper motor neuron versus a lower motor neuron lesion. Given the boy's neurologic examination findings, with absent reflexes, the paralysis is likely due to a condition affecting lower motor neurons. Some conditions to be considered are Guillain-Barre syndrome and transverse myelitis. One can distinguish among these conditions by performing an adequate neurologic examination.

Guillain-Barre syndrome, in particular, affects the peripheral nerves by demyelination. The classic presentation is a viral illness with an upper respiratory tract infection or gastrointestinal illness 1 to 2 weeks earlier, followed by a symmetrical ascending motor weakness. Lower extremities are affected more than upper extremities. Areflexia and paresthesia are also present.

Transverse myelitis is a neurologic condition that presents at a distinct motor or sensory level. Most patients presenting with transverse myelitis will have physical examination findings that point to a specific area of the spinal cord. This helps to differentiate Guillain-Barre syndrome and tick paralysis, which affects the nervous system more globally.

The Condition

Tick paralysis is caused by 2 major tick vectors in the United States: the dog tick and the wood tick. The female tick attaches onto its host and injects a neurotoxin that is believed to block acetylcholine release. In the United States, children and girls are more frequently affected than adults and boys, respectively. It is thought that girls are disproportionately affected because the tick remains unnoticed on the scalp due to their long hair. Its incidence is highest during mating season (February to August). Mortality of those affected by tick paralysis ranges from 6% to 13%. Seventy-nine percent of these deaths occur in children

younger than 16 years. Respiratory failure is the primary cause of mortality because of failure to recognize that the paralysis was caused by the tick bite and, therefore, delay in removal of the tick to prevent respiratory muscle paralysis.

Most affected children have nonspecific symptoms, including a 4- to 7-day prodrome of restlessness and irritability, followed by ascending paralysis. Bulbar lesions can be apparent on physical examination and may cause dysphagia and slurred speech. Local skin reactions have also been noted and are described as morbilliform rash. These rashes are different than the centripetal rash seen with Rocky Mountain spotted fever. Although symptoms of many parasite infections continue long after tick removal, tick paralysis symptoms resolve rapidly after removal of the tick.

Diagnosis

Characteristic signs and symptoms coupled with response to removal of the offending tick are enough to establish the diagnosis, and further evaluation is not necessary.

Management

Removal of the tick is the most important aspect of tick paralysis. Proper removal of the tick, including the head, which is usually lodged under the skin, will result in complete resolution of symptoms over a 24- to 48-hour period. A few case studies have reported weakness lasting up to 1 week.

To achieve proper removal of the engorged female tick, one must grasp the tick at the base of the head and remove. This can be accomplished with special tweezers that do not put pressure on the body of the tick. The most safe and efficient way to remove the tick is with tick keys, which slide over the body and, when pulled slowly sideways, removes the entire tick.

Education on how to properly remove ticks is vital, especially for those who live in areas where tickborne illnesses are prevalent. It is imperative to relay that burning and use of petroleum jelly products, 2 commonly used methods, are ineffective in tick removal. In addition, it has been reported that practitioners who removed ticks without gloves have developed transient paralysis.

Progression to respiratory compromise and failure will occur without removal of the offending tick. Patients who experience respiratory failure may need aggressive intervention, including intubation and ventilator support until the toxin effects subside.

To date, there is no evidence of other tickborne illnesses in patients with tick paralysis, and for this reason additional evaluation for tickborne illnesses is not recommended.

Lessons for the Clinician

- Tick paralysis is a relatively rare but easily diagnosed condition in children with acute-onset ascending paralysis.
- Children presenting with ascending paralysis should be carefully examined from head to toe, with care taken to fully examine hair-bearing areas, areas between toes, and in and around the ears.
- Signs of lower motor neuron paralysis, intact sensation, and resolution of paralysis on removal of the tick establish the diagnosis of tick paralysis.
- Proper removal of the tick is the mainstay of treatment.

Suggested Readings for this article are at <http://pedsinreview.aappublications.org/content/40/6/302>.

Suggested Readings

- Chagnon SL, Naik M, Abdel-Hamid H. Child neurology: tick paralysis: a diagnosis not to miss. *Neurology*. 2014;82(11):e91–e93
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Case 1: Progressive Weakness in a Previously Healthy 4-year-old Boy
Kristen Pontiff, Day Breen, Pamela McMahon, Cristina Zeretzke-Bien, Philip
Zachariah and Christopher Woodward
Pediatrics in Review 2019;40;302
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Index of Suspicion

2

A 2-month-old Girl with Liver Failure and a Brother with Tyrosinemia Type I

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PRESENTATION

A 2-month-old girl presents with jaundice, pallor, and abdominal distention. She was born by normal delivery at term weighing 2,380 g. Her 22-month-old brother has tyrosinemia type I detected on newborn screening (NBS) and subsequently confirmed by the presence of succinylacetone on a urine organic acid analysis and demonstration of homozygosity for the IVS8-1(g-c) mutation in the *FAH* gene. He is doing well and has normal liver function on standard treatment with NTBC (nitisinone) and a tyrosine- and phenylalanine-restricted diet. The parents are first cousins of Christian Arab origin from the north of Israel and confirmed to be heterozygous for the *FAH* mutation. Prenatal genetic diagnosis performed in the latest pregnancy on chorionic villus sampling indicated that the girl is a heterozygous carrier for the *FAH* mutation. Findings from her NBS were completely normal, including a negative test for succinylacetone. She is being bottle-fed with a regular infant formula.

On examination she looks pale and sweaty, although alert. Her abdomen is swollen but not tender, with a firm liver edge palpable below the costal margin, spleen not palpable. Initial laboratory results (Table) reveal a blood sugar level of 34 mg/dL (1.9 mmol/L), elevated hepatocellular and cholestatic liver enzyme levels, direct hyperbilirubinemia, hypoalbuminemia, and abnormal coagulation studies consistent with synthetic liver failure. She is treated with a glucose infusion and intramuscular vitamin K. In light of the family history and her presentation with synthetic liver failure, tyrosinemia type I is highly suspected despite the negative prenatal genetic testing and NBS. Urine organic acid analysis, indeed, reveals increased excretion of tyrosine metabolites, but succinylacetone is not detected. The results of her plasma amino acid profile (Table) suggest a different diagnosis.

DISCUSSION

Differential Diagnosis

Inborn errors of metabolism (IEMs) are an important cause of liver failure in neonates and young infants. (1) Many IEMs are treatable, including disorders of carbohydrate metabolism, such as galactosemia and hereditary fructose intolerance; disorders of amino acid metabolism and transport, such as tyrosinemia type

AUTHOR DISCLOSURE Drs Tal, Dar, Almashanu, Korman, and Dumin have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE. Laboratory Results

| TEST | PRETREATMENT | ON DIET 4 DAYS | ON DIET 2 MONTHS | REFERENCE RANGE |
|---|------------------------------|----------------|-------------------------|-----------------------|
| Glucose, mg/dL (mmol/L) | 34 (1.9) | 61 (3.4) | 76 (4.2) | 70–99 (3.9–5.5) |
| AST, U/L (μ kat/L) | 148 (2.47) | 90 (1.50) | 79 (1.32) | 5–34 (0.08–0.57) |
| ALT, U/L (μ kat/L) | 63 (1.05) | 45 (0.75) | 59 (0.99) | 0–55 (0–0.92) |
| GGT, U/L (μ kat/L) | 560 (9.35) | 617 (10.30) | 140 (2.34) | 9–36 (0.15–0.60) |
| Bilirubin, total, mg/dL (μ mol/L) | 6.10 (104) | 2.27 (38.8) | 0.64 (11.0) | 0.2–1.2 (3.42–20.5) |
| Bilirubin, direct, mg/dL (μ mol/L) | 4.39 (75.1) | 1.55 (26.5) | 0.36 (6.16) | 0–0.5 (0–8.55) |
| Albumin, g/dL (g/L) | 2.8 (28) | 2.9 (29) | 4.1 (41) | 3.8–5.4 |
| Total protein, g/dL (g/L) | 4.8 (48) | 4.5 (45) | 6.1 (61) | 6.4–8.3 |
| INR | 1.52 | 0.85 | | 0.8–1.2 |
| APTT, sec | 52.4 | | | 25–41 |
| α_1 -Fetoprotein, ng/mL (μ g/L) | 85,740 (85,740) ^a | | 924 (924) ^{bc} | ab |
| Fibrinogen, mg/dL (g/L) | 147 (1.47) | | | 157–360 (1.57–3.60) |
| Amino acids, mg/dL (μ mol/L) | | | | |
| Citrulline | 6.03 (344) | 0.65 (37) | 0.26 (15) | 0.11–0.88 (6–50) |
| Tyrosine | 7.12 (393) | 2.23 (123) | 1.09 (60) | 0.18–3.62 (10–200) |
| Phenylalanine | 1.85 (112) | 0.91 (55) | 0.73 (44) | 0.50–2.15 (30–130) |
| Methionine | 8.45 (566) | 8.42 (564) | 0.36 (24) | 0.22–0.97 (15–65) |
| Arginine | 8.22 (469) | 3.93 (224) | 1.75 (100) | 0.21–2.80 (12–160) |
| Lysine | 8.13 (556) | 7.03 (481) | 2.50 (171) | 1.46–5.26 (100–360) |
| Threonine | 7.00 (588) | 3.87 (325) | 2.48 (208) | 0.71–4.29 (60–360) |
| Serine | 2.85 (239) | 2.87 (241) | 1.54 (129) | 0.63–3.15 (60–300) |
| Threonine-to-serine ratio | 2.46 | 1.35 | 1.61 | ≤ 1.5 |
| Glutamine | 3.10 (212) | 7.5 (513) | 9.11 (623) | 5.70–14.6 (390–1,000) |

ALT=alanine aminotransferase, APTT=activated partial thromboplastin time, AST=aspartate aminotransferase, GGT= γ -glutamyltransferase, INR=international normalized ratio.

^a α_1 -Fetoprotein reference intervals for age 1 to younger than 3 months: 10 to 1,359 ng/mL (10–1,359 μ g/L).

^b α_1 -Fetoprotein reference intervals for age 3 to younger than 6 months: 4 to 275 ng/mL (4–275 μ g/L).

^c α_1 -Fetoprotein was 30 ng/mL (30 μ g/L) after 6 months of treatment.

I; the urea cycle disorders, including citrin deficiency; and fatty acid oxidation disorders. Other IEMs to consider include mitochondrial respiratory chain disorders, congenital disorders of glycosylation, transaldolase deficiency, and Niemann-Pick type C disease. In this patient, tyrosinemia type I was suspected because of the history of an affected sibling but was unlikely in view of the negative testing for succinylacetone. Nevertheless, rare cases of tyrosinemia type I with undetectable succinylacetone have been reported. (2) Particularly in the context of parental consanguinity, the possibility of a second IEM in the same family also needs to be considered.

Actual Diagnosis

Plasma amino acid analysis revealed elevated citrulline, arginine, threonine, lysine, and methionine levels; low glutamine levels; and an elevated threonine-to-serine ratio (Table). α_1 -Fetoprotein level was markedly elevated. These findings were highly suggestive of citrullinemia type II, also known as citrin deficiency. Sequencing of the citrin-encoding gene *SLC25A13* revealed a novel homozygous c.848G>T p.G283V mutation predicted to be pathogenic.

The Condition

Citrin, an aspartate-glutamate mitochondrial inner membrane transporter, is defective in citrullinemia type II. Citrin is essential

for normal functioning of the urea cycle by providing aspartate for the synthesis of argininosuccinic acid (Fig). Citrin is also an important component of the malate-aspartate transporter, which transports cytosolic NADH from glycolysis into the mitochondria. Carbohydrate ingestion causes an increase in the cytosolic NADH/NAD⁺ ratio, which inhibits aerobic glycolysis in cells, leading to energy shortage in hepatocytes and suppression of ureogenesis. Furthermore, increased NADH also impairs galactose metabolism, leading to accumulation of other toxic compounds in hepatocytes, similar to galactosemia.

The clinical phenotype of citrin deficiency varies according to the age at onset. (3) The neonatal/infantile form presents with transient intrahepatic cholestatic hepatitis, whereas the late adolescence or adult form presents with neuropsychiatric symptoms associated with hyperammonemia. In the intervening period, affected children may be apparently asymptomatic but have failure to thrive, dyslipidemia, fatty liver, and aversion to carbohydrates. (4)

Infants may present with prolonged cholestatic jaundice and failure to thrive, accompanied by hypoalbuminemia, abnormal coagulation profile, liver dysfunction, hypoglycemia, hemolytic anemia, and hypergalactosemia. The plasma amino acid profile shows elevation of not only citrulline but also arginine, methionine, tyrosine, and threonine levels, with an elevated threonine-to-serine ratio. Citrin deficiency might be detected on NBS by elevation of any of the previously mentioned amino acids or as a false-positive for galactosemia screening. However, only approximately 40% of infants with citrin deficiency have an abnormal NBS result. (5) In Israel the proportion is likely to be even lower

because galactosemia is not included in the national NBS program. Diagnosis is confirmed by mutation analysis of the *SLC25A13* gene.

Treatment/Management

Treatment with a lactose-free formula, as in galactosemia, and provision of medium-chain triglycerides (MCTs) as an alternative source of energy to the hepatocytes should be initiated as soon as the diagnosis of citrin deficiency is suspected in cholestatic infants. (6) After the first year of life, a low-carbohydrate, high-protein, and high-fat diet, as preferred by the patients, is recommended. Administration of arginine, sodium pyruvate, and/or MCTs may be beneficial. Liver transplant may be required to prevent the hyperammonemic episodes and correct the metabolic disturbances. (7)

Patient Course

Once citrin deficiency was suspected, glucose infusion was ceased and she was started on a lactose-free formula enriched with additional MCTs. Repeated blood tests showed improvement in hepatocellular and cholestatic liver enzyme levels and blood albumin levels, resolution of her direct hyperbilirubinemia, and normalization of her coagulation studies (Table). She maintained normoglycemia when fed every 3 hours. She was discharged from the hospital after 5 days in good general condition. She is now 7 months of age and continues regular follow-up in the Metabolic Clinic. She has mild global developmental delay and hypotonia. Her weight and height are between the 5th and 10th percentiles for age.

Lessons for the Clinician

- Two different rare inherited inborn errors of metabolism (IEMs) with overlapping phenotypes may occur in the same family, particularly if there is parental consanguinity, leading to diagnostic confusion.
- Prompt recognition and accurate diagnosis of treatable IEM causing liver disease in infancy is crucial for initiation of early lifesaving treatment.
- Citrin deficiency presents in neonates or young infants as intrahepatic cholestasis with low birthweight, hepatomegaly, liver dysfunction, hypoproteinemia, coagulopathy, and/or hypoglycemia.
- The characteristic laboratory findings include an amino acid profile with elevated citrulline, methionine, arginine, tyrosine, and phenylalanine levels, together with galactosemia and markedly elevated α -fetoprotein.
- Whereas patients with citrullinemia type I and other urea cycle disorders require a low-protein, high-carbohydrate diet, patients with citrullinemia type II develop an

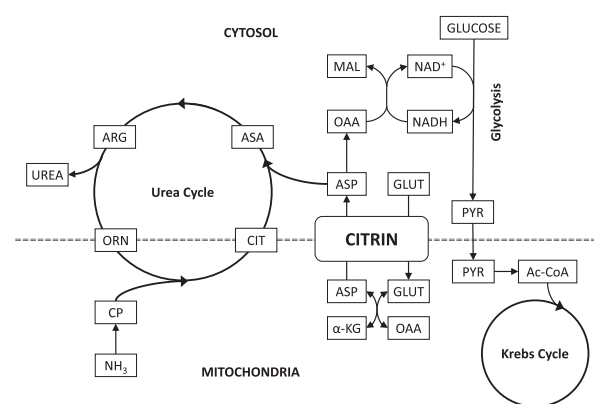


Figure. Role of citrin, an aspartate glutamate carrier, located on the inner mitochondrial membrane of the hepatocytes, involved in ureogenesis by supplying aspartate for the formation of argininosuccinic acid in the urea cycle and an important component of the malate-aspartate transporter, which transports cytosolic NADH from glycolysis into the mitochondria. α -KG=alpha-ketoglutarate, Ac-CoA=acetyl-CoA, ARG=arginine, ASA=argininosuccinic acid, ASP=aspartate, CIT=citrulline, CP=carbamoyl phosphate, GLUT=glutamate, MAL=malate, NH₃=ammonia, OAA=oxaloacetate, ORN=ornithine, PYR=pyruvate.

aversion to carbohydrates and respond to a diet high in protein and fat and low in carbohydrates.

- Citrin deficiency may be detected by newborn screening (NBS), but only in a minority of cases. Clinicians need to be aware of the disorders included in their regional NBS

program and the limitations in detection of tyrosinemia type I and citrin deficiency by NBS.

References for this article are at <http://pedsinreview.aappublications.org/content/40/12/639>.

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Case 2: A 2-month-old Girl with Liver Failure and a Brother with Tyrosinemia Type I

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2 A 2-year-old Girl with Difficulty Bearing Weight

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AUTHOR DISCLOSURE Drs Vander-Plas and Eboh have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 2-year-old girl is transferred to our facility due to the inability to bear weight. On the previous day, she had normal development and received her hepatitis A vaccine at her pediatrician's office. A complete blood cell count, electrolytes, liver function tests, kidney function tests, C-reactive protein level, erythrocyte sedimentation rate, and magnetic resonance imaging (MRI) of the lumbar spine performed before transfer were normal. Results of cerebrospinal fluid (CSF) studies, urinalysis, and creatine kinase measurement performed on arrival were normal. Her condition rapidly progressed to include truncal ataxia, nystagmus, and upper extremity weakness with **out** deep tendon reflexes. Further evaluation confirmed the diagnosis.

DISCUSSION

Based on presentation and rapid progression, a diagnosis of Guillain-Barré syndrome (GBS) was entertained. An MRI of the brain and spine was obtained and showed abnormal enhancement along the nerve roots of the cauda equina. Nerve conduction studies showed decreased response of the proximal nerves. She received intravenous immunoglobulin and remained hospitalized for 6 days, with gradual improvement.

Differential Diagnosis

Our differential diagnosis initially included trauma due to an occult fracture, infection, tick paralysis, acute flaccid myelitis, and GBS. Findings from plain radiographs of her knee and pelvis, complete blood cell count, and CSF studies were normal, eliminating traumatic and infectious etiologies. There was no history of travel to regions with tick populations, and no ticks were present on the patient. There was also no history of recent illness, ruling out acute flaccid myelitis as a likely source. As the presentation evolved, GBS moved to the top of the differential diagnosis list.

The Condition

Guillain-Barré Syndrome. Because young children commonly present with symptoms such as **leg pain, weakness, and inability to bear weight**, GBS should be strongly considered in these patients. As the disease progresses, the torso,

arms, and muscles of respiration become involved, and this can lead to respiratory failure. Children may also have **autonomic dysfunction or intestinal ileus**. (1) Guillain-Barré syndrome presents as an acute ascending paralysis, often provoked by a preceding illness, causing **demyelination of peripheral nerves**. Incidence ranges from 0.3 to 1.3 cases per 100,000 in patients younger than 18 years, with boys being 1.5 times more likely to be affected than girls. (2)

Diagnosis. Primarily a **clinical diagnosis**, ancillary testing is used only to confirm the diagnosis. Testing includes **CSF studies** (elevated protein level with a normal white blood cell count), **electromyography**, **MRI** of the spine (shows enhancement of nerve roots and cauda equine [3]), and **antibody studies**. (4)

Management. With treatment, the course of the illness lasts approximately **2 to 4 weeks**, a shorter duration than in most adults. (5) Treatment includes close monitoring and supportive care. (4) Immunologic treatment, including **intravenous immunoglobulin and/or plasmapheresis**, should be considered in severe, progressive cases. (5) Corticosteroids are **ineffective**. (6) We did not believe that her symptoms were due to the hepatitis A vaccine. A study in 2012 regarding the topic of hepatitis vaccination and GBS found the incidence to be similar to that seen in the

general population, indicating that there is unlikely to be a link between the two. (7) As clinicians, it is imperative that we educate our patients on the necessity and benefit of vaccinations, as well as the extreme rarity of vaccine complications.

Lessons for the Clinician

- In patients who present with lower extremity pain, weakness, and inability to walk, Guillain-Barré syndrome should be strongly considered.
- Although mild cases may simply need observation and supportive care, early diagnosis and treatment of rapidly progressive cases is critical to prevent respiratory compromise.
- Guillain-Barré syndrome is a rare complication of only a few vaccines, and the benefits outweigh the risk in most cases; there does not seem to be a link between this syndrome and hepatitis vaccination.

NOTE. This case is based on a presentation by Stephanie Vander-Plas, MD, and Ngozi Eboh, MD, at the Pediatric Hospital 2017 Conference, Nashville, Tennessee, Poster Session #1, Poster #154, July 20, 2017.

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2 Agitation and Abnormal Movements in a 14-year-old Boy

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PRESENTATION

A 14-year-old boy with attention-deficit/hyperactivity disorder, depression, autism spectrum disorder, and astrocytoma (status-post resection in infancy, no residual deficits) presents to the emergency department (ED) with 2 days of abnormal movements: facial twitching, jaw stiffness, and torticollis, progressing to whole-body tremors, agitation, diaphoresis, and altered mental status. Medications include fluoxetine 60 mg daily and lisdexamfetamine 60 mg daily, started 1 year ago. He recently gained independence with taking medications but took no medications in the past week. Two days ago his mother discovered his noncompliance and restarted his medications at the prescribed doses. Since symptom onset, he was seen in community EDs twice, received diphenhydramine for dystonia and lorazepam for agitation, and was discharged.

Vital signs are temperature, 98.8°F (37.1°C); blood pressure, 121 to 149/64 to 76 mm Hg; heart rate, 70 to 90 beats/min, with episodes of 170 beats/min when tremulous; respirations, 18 to 24 breaths/min; and oxygen saturation, 97% to 99% on room air. He is diaphoretic and agitated; his eyes are closed, but he opens them on command. He responds to questions verbally and follows commands. He has rotary and horizontal nystagmus, right-sided torticollis, and brisk reflexes. He has episodes of bilateral lower extremity hypertonia and tremors lasting 15 to 30 seconds, up to 5 episodes per hour. His Glasgow Coma Scale score is 14 (–1 for eyes).

An electrocardiogram shows normal sinus rhythm. Laboratory results include a white blood cell count of 5,840/ μ L (5.84×10^9 /L), a hemoglobin level of 13.1 g/dL (131 g/L), a platelet count of 239 $\times 10^3$ / μ L (239×10^9 /L), a lactate level of 12.61 mg/dL (1.4 mmol/L), and a creatine kinase level of 91 U/L (1.52 μ kat/L). Head computed tomography shows no acute intracranial abnormality and unchanged postoperative findings. A clinical diagnosis is made.

DISCUSSION

Hospital Course

Our patient's constellation of symptoms, diaphoresis, intermittent tachycardia with tremors, hypertension, hyperreflexia, right-sided abnormal movements, and

AUTHOR DISCLOSURE Drs Pande, O'Halloran, and Nguyen have disclosed no financial relationships relevant to this article. Dr Stewart has disclosed that she is the project director for a Health Resources and Services Administration grant to improve health-care delivery for people with sickle cell disease. Dr Canares has disclosed that she is a grant recipient for a research project involving offering dental screenings and preventive services through the joint collaboration of the Johns Hopkins–Walgreens Committee. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

rotary nystagmus (later identified as ocular clonus), in addition to history of exposure to a selective serotonin reuptake inhibitor plus lisdexamfetamine (which has serotonergic activity), prompted a diagnosis of serotonin syndrome. His symptoms met the Hunter Serotonin Toxicity Criteria for a case of mild to moderate serotonin syndrome (Fig). (1) He received 4 mg of oral cyproheptadine, and within 30 minutes he had resolution of episodic tremors, diaphoresis, ocular clonus, tachycardia, and hypertension but had no improvement in mental status (persistent eye-opening and speech in response to verbal stimuli, but not spontaneously). Due to ongoing mental status changes, the Poison Control Center advised administering cyproheptadine 2 mg every 2 hours, as needed. He received 2 mg of oral cyproheptadine 2 hours after the first dose and subsequently became more difficult to arouse (eye-opening and speech to painful stimuli), although his tremors, clonus, and vital sign abnormalities continued to improve. Given that the rest of his examination findings substantially improved after administration of cyproheptadine, it is thought that his increased sleepiness was an expected adverse effect from the anticholinergic properties of cyproheptadine. He was admitted to the hospital for management of serotonin syndrome.

During his admission, cyproheptadine administration was discontinued. His symptoms gradually improved over 36 to 48 hours with supportive care, his neurologic and mental status examinations returned to baseline, and he was discharged 48 hours after admission. The remainder of the evaluation findings, including brain magnetic resonance imaging and electroencephalography, were normal. Psychiatry advised holding all psychiatric medications until the next outpatient appointment.

Background

Serotonin syndrome is defined as the triad of acute altered mental status, autonomic instability, and neuromuscular abnormalities associated with the initiation or increase in dosage of a serotonergic agent. (2) Symptoms can last for days after serotonin syndrome onset. Classically, serotonin syndrome is thought to develop in patients after an increased dose or overdose of serotonergic agents. However, it is important to recognize that its presentation may be unpredictable because it can occur with therapeutic dosing. (2)(3) Furthermore, exposure to lisdexamfetamine, which has an affinity for the serotonin receptor, is reported as a risk factor for serotonin syndrome. (4)(5) The spectrum of clinical manifestations is mediated by excessive stimulation

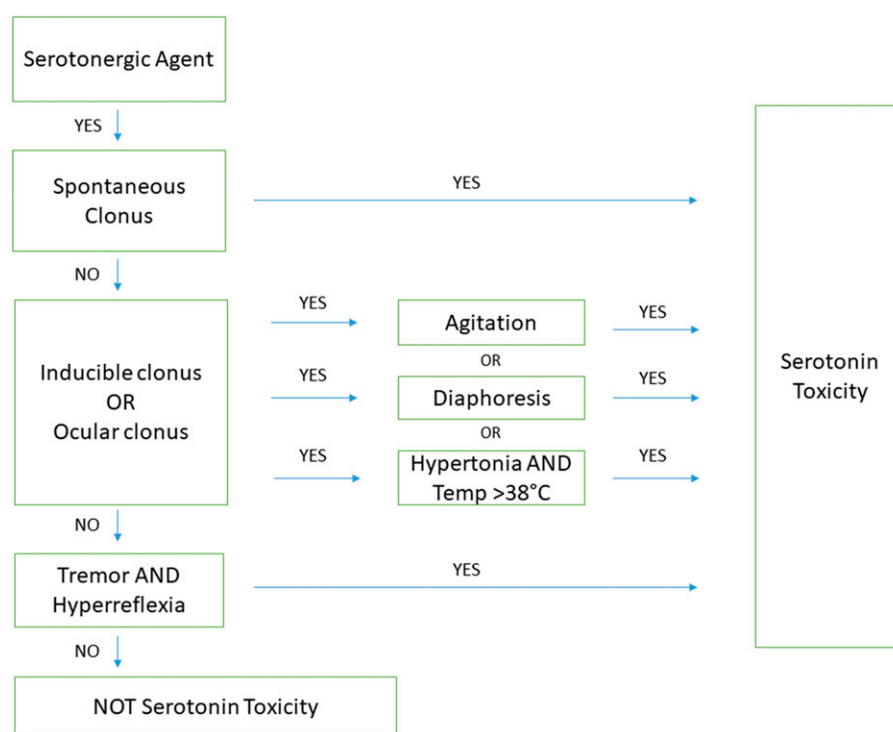


Figure. The Hunter Serotonin Toxicity Criteria. (Adapted with permission from Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *QJM*. 2003;96(9):639.)

of central and peripheral serotonin receptors, ranging from barely perceptible to lethal. (2)(6)

Differential Diagnosis

The differential diagnosis in the patient with neurologic or mental status changes and elevated temperature, heart rate, or blood pressure includes anticholinergic syndrome, malignant hyperthermia, and neuroleptic malignant syndrome. These diagnoses can be differentiated by a thorough history and physical examination. (7) Laboratory tests or diagnostic imaging should be used to rule out diagnoses with similar symptoms. (7) Diagnosis of serotonin syndrome may be difficult due to the variability of clinical symptoms and the potentially indolent course of the syndrome, leading patients to seek delayed care. (8)(9) Furthermore, pediatric physicians may not immediately recognize the constellation of symptoms because it is more frequently reported in adults. (8)(10)

Treatment

The mainstay of therapy for serotonin syndrome is removal of the offending serotonergic drugs and supportive care. (7)(10) Most serotonergic drugs are metabolized to their active metabolite in the liver and are renally cleared. (11) Mild cases of serotonin syndrome may resolve within 24 to 72 hours with discontinuation of offending drugs and supportive care; however, symptoms may persist for longer in patients taking drugs with longer half-lives. Mild cases may be observed in the ED for 4 to 6 hours or may require a 12- to 24-hour admission, until mental status, vital signs, and neurologic symptoms resolve. Moderate to severe cases with hyperthermia, autonomic instability, or progressive cognitive changes require hospitalization. (2)(7) Treatment should focus on management of airway, breathing, and circulation. Fluids for correction of vital signs are used, as well as benzodiazepines for control of agitation and tremors. (12) Cyproheptadine is the recommended antidote to serotonin syndrome. Cyproheptadine is a histamine-1 receptor antagonist and has antagonistic properties to the serotonin receptors 5-HT_{1A} and 5-HT_{2A}. (13) Strong

evidence of its efficacy in serotonin syndrome is lacking because the literature is limited to case series. (7)(10) Expected adverse effects of cyproheptadine include hypotension and sedation. (13) In severe cases, hyperthermia (temperature >106°F [$>41.1^{\circ}\text{C}$]) due to excessive muscle contractions should be treated with sedation, neuromuscular paralysis, and endotracheal intubation. (2)(14) There is no role for antipyretic agents because the hyperthermia is due to increased muscular activity and not a change in the hypothalamic set point. (2)(15) Furthermore, physical restraints should be avoided in agitation because muscle contractions can exacerbate hyperthermia. (14)

In summary, this case highlights a classic presentation of an uncommon diagnosis of serotonin syndrome in an adolescent who abruptly stopped and restarted his fluoxetine and lisdexamfetamine. His symptoms significantly improved after administration of a single dose of cyproheptadine, adding to the limited body of literature of the efficacy of this antidotal agent. Clinicians must maintain an index of suspicion for serotonin syndrome in the patient with tremor, agitation, diaphoresis, and exposure to selective serotonin reuptake inhibitors and amphetamines.

Lessons for the Clinician

- Prescribers of antidepressants and amphetamines must provide their patients with specific anticipatory guidance regarding the risks of abruptly discontinuing and restarting these medications.
- Medication compliance should be monitored closely in patients who are at risk for taking their medications erratically, such as adolescent patients.
- It is critical to maintain a high index of suspicion for serotonin syndrome in all patients with unexplained altered mental status who have a history of selective serotonin reuptake inhibitor and amphetamine exposure.
- Although evidence of cyproheptadine therapy is lacking, this case demonstrates its efficacy in an adolescent patient.

References for this article are at <http://pedsinreview.aappublications.org/content/40/10/532>.

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Index of Suspicion

2 Respiratory Failure and Multiple Organ System Dysfunction in a 7-day-old Infant

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PRESENTATION

A 7-day-old boy is referred to the emergency department by his pediatrician for increased work of breathing. He was born at 39 weeks' gestation by spontaneous vaginal delivery with prolonged rupture of membranes. His newborn nursery stay was uncomplicated, and the results of his congenital heart screen were normal. His mother reports difficulties with breastfeeding due to poor latch, for which he has been receiving supplemental formula. She also reports increased fussiness and "brownish-red spots" in his diapers. There is no cyanosis or choking during feeds. There is no history of fever, vomiting, diarrhea, rashes, cough, sick contacts, or decreased urine output.

On examination he is alert, afebrile, and mildly tachycardic, with a blood pressure (BP) of 70/22 mm Hg. Weight is 3,270 g (birthweight, 3,785 g). Oxygen saturation is 84% on room air and improves to 98% with supplemental oxygen. He is tachypneic, with subcostal retractions, grunting, and head bobbing during respirations. Lungs are clear to auscultation. Capillary refill is normal, and femoral pulses are strong. There are no rashes. Abdomen is soft, with mild hepatosplenomegaly.

Laboratory evaluation is notable for a white blood cell count of 28,000/ μ L (28×10^9 /L), blood urea nitrogen level of 42 mg/dL (15.0 mmol/L), and creatinine concentration of 0.72 mg/dL (63.65 μ mol/L). Results of cultures and viral studies are pending. Liver enzyme levels, troponin level, B-type natriuretic peptide level, prothrombin time, and D-dimer level are significantly elevated; ammonia level is 96.6 μ g/dL (69 μ mol/L). A capillary blood gas analysis shows mixed respiratory and metabolic acidosis with an elevated lactate level. A urine dipstick test shows 3+ protein, large blood, and nitrites, with white and red blood cells.

A chest radiograph demonstrates cardiomegaly and increased pulmonary vascularity (Fig 1). An echocardiogram reveals no patent ductus arteriosus or structural heart disease but is significant for moderate biventricular systolic depression and dilation with severe pulmonary arterial hypertension.

He is admitted to the PICU on broad spectrum antibiotics and high-flow nasal cannula for oxygen supplementation. Milrinone therapy is initiated due to depressed ventricular function. His BP subsequently increases to 127/89 mm

AUTHOR DISCLOSURE Drs Poisson, Lin, Chen, and McCrory have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

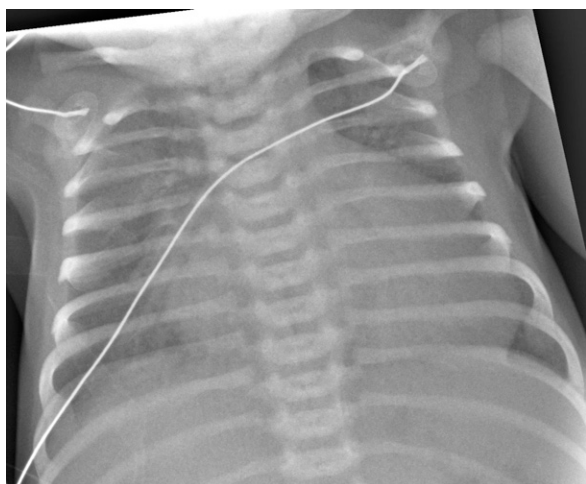


Figure 1. Chest radiograph demonstrating marked cardiomegaly with diffusely increased pulmonary vascularity.

Hg and is sustained. Within hours he is intubated due to worsening hypoxic respiratory failure. A subsequent imaging study reveals the cause of his multiorgan failure.

DISCUSSION

Hospital Course

This 7-day-old boy presented with multiorgan dysfunction, including hypoxic respiratory failure, heart failure (as evidenced by echocardiographic findings and hepatosplenomegaly), acute kidney injury (as evidenced by an elevated serum creatinine level for age and the presence of hematuria and proteinuria), and highly elevated liver enzyme levels with coagulopathy. The team initially suspected urosepsis as the underlying etiology based on urinary findings and clinical presentation. Other differential diagnoses included sepsis of another etiology, congenital heart disease, myocarditis, congenital viral infection, or metabolic disorder (such as organic acidemia, fatty acid oxidation defect, or mitochondrial disorder). Viral myocarditis with associated cardiac dysfunction remained a possibility, but results of viral studies (including herpes simplex virus from blood and cerebrospinal fluid, adenovirus from blood and urine, enterovirus from blood, and respiratory viral panel from nasal swab) were negative. Blood, urine, and cerebrospinal fluid cultures were also negative. Metabolic disorder was less likely given the absence of significant hyperammonemia, dysmorphism, or hypotonia, as well as rapid clearance of lactate. The newborn screen was later found to be normal except for a borderline acylcarnitine profile, which was not repeated due to the discovery of an alternate definitive diagnosis.

Renal ultrasonography was performed due to concern for urinary tract infection in a newborn. It showed an enlarged, echogenic left kidney and a possible partly duplicated right collecting system. Nephrology was consulted owing to these findings and a persistently elevated BP (>99th percentile for postconceptional age). (1) Four-extremity BPs were congruent. Repeated urinalysis on day 3 of admission showed only 3+ proteinuria and large blood with negative microscopic examination. Concern was raised for renovascular hypertension, and duplex ultrasonography of renal vasculature revealed critical stenosis of the left renal artery. Mesenteric duplex ultrasonography and magnetic resonance angiography were also performed, with magnetic resonance angiography (Fig 2) confirming the presence of left mid-distal renal artery stenosis with no other vascular anomalies. Plasma renin activity and aldosterone level were significantly elevated: renin, 1,333 ng/mL per hour (reference range, 2.35–37 ng/mL per hour), and aldosterone, 295 ng/dL (8,183 pmol/L) (reference range, 5–31 ng/dL [139–860 pmol/L]).

The Condition

Neonatal hypertension occurs in approximately 0.2% of neonates, where renovascular and renal parenchymal abnormalities constitute most cases. (2) Indwelling umbilical arterial catheter with associated thromboembolism is a common etiology; however, our patient had an umbilical

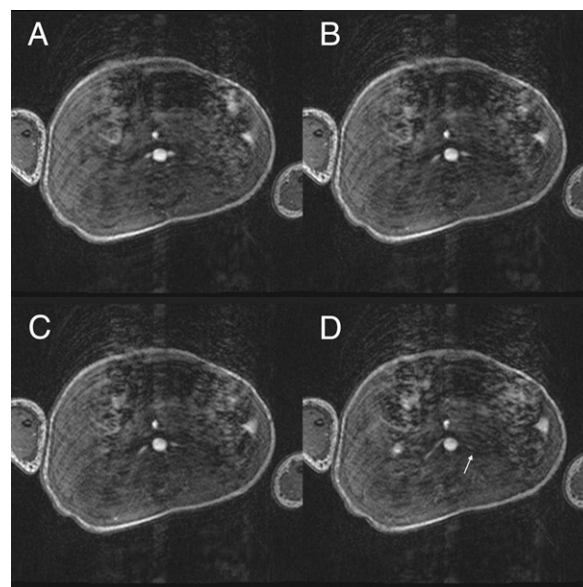


Figure 2. Magnetic resonance angiogram of the renal arteries using two-dimensional time-of-flight imaging. The renal arteries are followed from their abdominal aorta origin in sequential images A to D, with similar caliber observed bilaterally in the proximal images A to C. Attenuation of signal is noted in the mid-distal left renal artery in image D (arrow), indicating stenosis.

line placed only after his initial presentation. Diagnostic evaluation for neonatal hypertension should be targeted at identifying possible underlying etiologies, beginning with 4-extremity BP to rule out aortic coarctation. (1) If underlying or secondary cardiac pathology is suspected, chest radiography and echocardiography may be useful. Abdominal examination should assess for flank masses or abdominal bruits. Laboratory evaluation may include complete blood cell count, electrolytes, blood urea nitrogen, creatinine, urinalysis, fractional excretion of sodium, thyrotropin and free T₄, plasma fractional metanephrines and catecholamines, plasma renin activity, aldosterone, and cortisol to assess for intrinsic renal etiology, hyperthyroidism, pheochromocytoma, or congenital adrenal hyperplasia. Imaging should begin with renal ultrasonography with Doppler study to search for congenital renal anomaly or mass. Additional imaging studies may be needed, including abdominal computed tomography, vesicoureterography, magnetic resonance imaging/magnetic resonance angiography, or renal angiography to define renal/adrenal masses or vascular/urologic anomalies.

Renal artery stenosis is uncommon in the neonatal population and often presents with hypertension. In the setting of decreased renal perfusion pressure, the renin-angiotensin system is activated, causing vasoconstriction and aldosterone release with subsequent salt/water retention and hypertension. If uncontrolled, increased afterload and resulting cardiac strain can precipitate heart failure and pulmonary edema. Although no BPs were recorded in our patient's newborn nursery stay, we postulate that this mechanism was responsible for his presentation. Such cases have been described that presented with respiratory failure, heart failure, nephrotic syndrome, or a sepsislike picture. (3)(4)(5)(6)(7) Other renal anomalies, such as renal tubular dysgenesis, may exhibit a similar presentation. (8) Note that hypertension may not manifest until the presenting congestive heart failure or shock is addressed. (3) Our patient's BP rose from 70/22 mm Hg at presentation to 127/89 mm Hg with the administration of maintenance fluids, supplemental oxygen, and milrinone therapy. Renal artery stenosis in a pediatric population has also been described in association with congenital rubella, (9) neurofibromatosis 1, (10) tuberous sclerosis complex, (11) neuroblastoma, (12)

retroperitoneal hematoma, (13) fibromuscular dysplasia, (3) and midaortic syndrome. (14)

Infants with BP greater than the 99th percentile for postconceptional age and signs of hypertensive emergency, such as encephalopathy, acute kidney injury, cardiac failure, or vascular injury, should receive continuous infusion of intravenous antihypertensive medications, such as nicardipine, labetalol, or esmolol. Once BP is better controlled, the patient can be transitioned to oral therapy. (15) Surgical nephrectomy may be curative if BP is unresponsive to medication.

Our patient's hypertension responded to a nicardipine drip. During his hospitalization, his acute kidney injury resolved, cardiac function improved, and he was extubated and weaned to room air. He was discharged on 0.2 mg/kg amlodipine twice daily and 0.04 mg/kg enalapril twice daily. At 2-month follow-up, his BP remained well-controlled, cardiac function had normalized, and renal function and urinalysis were normal.

Lessons for the Clinician

- Renal artery stenosis should be on the differential diagnosis of an infant with congestive heart failure in the absence of congenital heart disease.
- In the setting of heart failure due to severe arterial hypertension, elevated blood pressures may not be readily apparent until cardiac function improves.
- Signs of neonatal hypertension may initially be non-specific, including feeding difficulties, irritability, apneas, seizure, or failure to thrive.
- Initial evaluation for neonatal hypertension should include 4-extremity blood pressures, chest radiography, echocardiography, complete blood cell count, electrolytes, blood urea nitrogen and creatinine, urinalysis with urine protein to creatinine ratio, thyroid function, and renal ultrasonography with Doppler study. Further evaluation should be guided by initial findings and clinical suspicion.
- Infants with sustained blood pressures greater than the 99th percentile for postconceptual age and signs of hypertensive emergency require continuous intravenous infusion of antihypertensive medications.

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2 A 4-year-old Boy with Recurrent Vomiting

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PRESENTATION

A 4-year-old boy presents with recurrent episodes of vomiting over a 2-month period. The vomit is nonbloody, nonbilious, and not associated with diarrhea or fever. There seems to be no specific pattern to the vomiting, although the patient's father suspects that it is the result of eating too many potato chips. Accompanying symptoms include a 2-lb (907-g) weight loss, fatigue, and darkening of eczematous lesions. His medical history includes eczema, constipation, and hospitalization at age 6 weeks for vomiting, failure to thrive, hyponatremia, and hyperkalemia, which were attributed to a urinary tract infection and improper formula mixing. The evaluation at that time showed normal renal ultrasonography and voiding cystourethrography findings. His family history reveals a 26-year-old male maternal first cousin who presented with similar symptoms as a young child and is now being treated with testosterone for delayed puberty. In addition, 4 maternal uncles passed away during infancy because of reported infections and high fever. A maternal aunt passed away at 2 years of age from an unknown cause. The patient is mildly tachycardic (heart rate, 102 beats/min) and normotensive (blood pressure, 91/57 mm Hg). His temperature is 97°F (36.1°C), and respirations are 18 breaths/min. Physical examination shows hyperpigmented macules over the right antecubital fossa, left gluteal region, perioral region, and gums; the remainder of the examination findings are normal. Laboratory studies show hyponatremia (sodium level of 124 mEq/L [124 mmol/L]), hypochloremia (chloride level of 94 mEq/L [94 mmol/L]), and metabolic acidosis (carbon dioxide level of 17 mEq/L [17 mmol/L]). Glucose, potassium, and calcium levels are normal. His cortisol level at 8 AM is low (6.7 µg/dL [184.9 nmol/L]), and his corticotropin level is significantly elevated (2,368 pg/mL [521 pmol/L]; reference range, 9–57 pg/mL [2–12.5 pmol/L]), as is the plasma renin level (48,600 pg/mL [1,151.8 pmol/L]; reference range, 250–5820 pg/mL [5.9–137.9 pmol/L]). Additional testing reveals the diagnosis.

DISCUSSION

A corticotropin stimulation test shows cortisol levels of 3.4, 3.5, and 3.4 µg/dL (93.8, 96.6, and 93.8 nmol/L) at 0, 30, and 60 minutes, respectively. Peak cortisol levels less than 18 µg/dL (<496.6 nmol/L) 30 and 60 minutes after the administration of cosyntropin are consistent with a diagnosis of adrenal insufficiency. (1) The initial clinical presentation, along with corticotropin level, can

AUTHOR DISCLOSURE Drs Jain and Karaviti have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

help providers differentiate between primary (adrenal cortical disease) and secondary (pituitary disease) adrenal insufficiency. Primary disease causes a low cortisol level with a subsequent elevation of corticotropin because of feedback mechanisms, and secondary disease causes a low corticotropin level, which results in a low cortisol level. Our patient has a low cortisol level, an elevated corticotropin level, and evidence of salt wasting and hyperpigmentation on examination, all consistent with primary adrenal insufficiency. To evaluate the etiology of primary adrenal insufficiency, 17-hydroxyprogesterone, 21-hydroxylase antibody, and very long-chain fatty acid analysis are performed, and the results are within the reference range. Given the family history, which is suggestive of an X-linked disease (Fig), genetic testing is performed for the *NROB1* gene. The result reveals a pathogenic variant of the *NROB1* gene, which is diagnostic for X-linked congenital adrenal hypoplasia. (2) The patient receives intravenous fluid replacement and is started on “stress-dose” hydrocortisone (100 mg/m² per day). With clinical improvement, hydrocortisone is decreased to “triple dose” (30 mg/m² per day), and fludrocortisone (0.1 mg twice a day) is started. Once back at his baseline status, the patient is sent home on maintenance hydrocortisone (10 mg/m² per day) and fludrocortisone, and the family is taught sick-day management for adrenal insufficiency. With appropriate treatment, follow-up laboratory test results show normalization of electrolyte, corticotropin, and plasma renin levels, and hyperpigmentation improves

significantly. He is currently thriving as a healthy child with normal weight and linear growth that is within his genetic potential.

The Condition

Congenital adrenal hypoplasia, also known as adrenal hypoplasia congenita, is a rare condition with a reported incidence of 1 in 12,500 births. (2) Most affected individuals present in the first few months of life with failure to thrive, hyponatremia, hypoglycemia, and hyperpigmentation. Early diagnosis and treatment are imperative and can prevent sudden death. (3) Older individuals may present with a preference for salty foods (eg, potato chips) and with concomitant illness that precipitates adrenal failure. Hypogonadotropic hypogonadism is commonly associated with congenital adrenal hypoplasia, and patients can present with cryptorchidism, delayed or arrested puberty, and infertility. (2) Congenital adrenal hypoplasia results from mutations in the *NROB1* gene, which encodes DAX1 on chromosome Xp21. (2)(4)(5) Of note, deletions in Xp21 can cause a contiguous gene syndrome with congenital adrenal hypoplasia that involves glycerol kinase deficiency and Duchenne muscular dystrophy. (6) As seen in our patient, a positive family history consistent with X-linked inheritance is likely to reveal a pathogenic variant in *NROB1* in almost 100% of affected individuals. (2) Genetic counseling that addresses carrier status and recurrence risks should be provided.

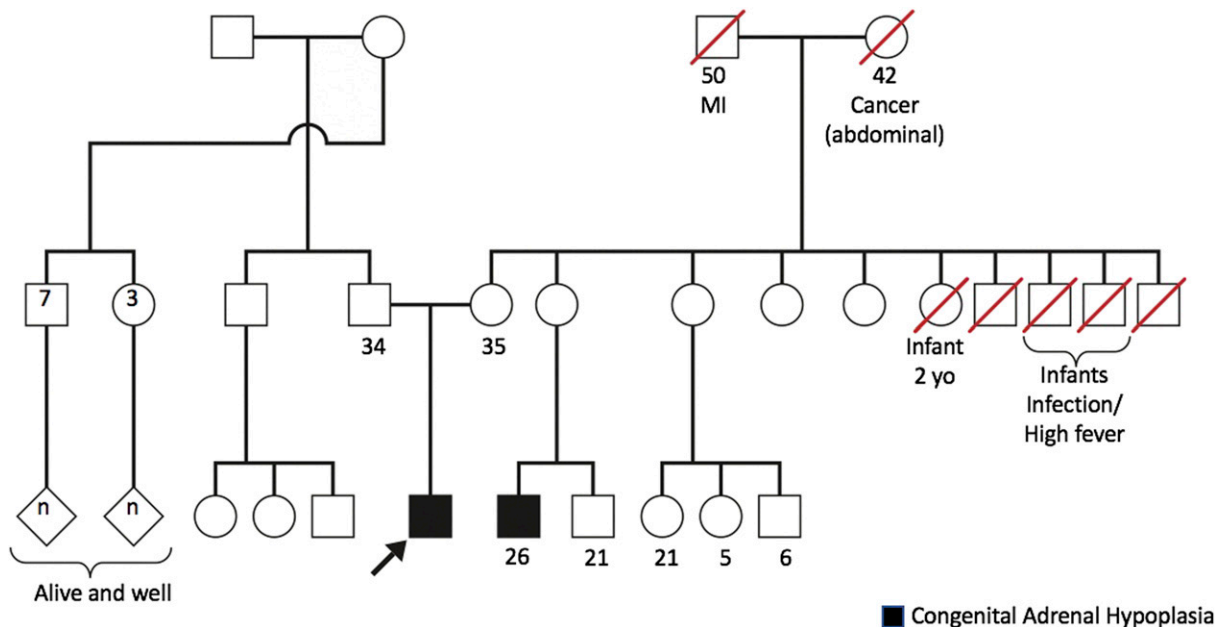


Figure. Pedigree reveals the proband (black arrow) and a male maternal first cousin with congenital adrenal hypoplasia. Four maternal uncles passed away during infancy due to reported infections and high fever. A maternal aunt passed away at 2 years of age from an unknown cause.

Differential Diagnosis

When the diagnosis of adrenal insufficiency is established, the underlying etiology, whether primary or secondary, should be sought. Both primary and secondary adrenal insufficiency can present with symptoms of glucocorticoid deficiency, which include fatigue, nausea, vomiting, fasting hypoglycemia, and decreased free water clearance, which can cause mild hyponatremia. However, only primary adrenal insufficiency will present with mineralocorticoid deficiency (hyponatremia, hyperkalemia, metabolic acidosis) and hyperpigmentation (due to a stimulant effect of elevated corticotropin levels). Important endocrine causes of primary adrenal insufficiency include congenital adrenal hypoplasia (*NROB1* mutation), congenital adrenal hyperplasia (elevated 17-hydroxyprogesterone level), Addison disease (a positive 21-hydroxylase antibody test result), adrenoleukodystrophy (high levels of very long-chain fatty acids), and autoimmune polyglandular syndrome (*AIRE-1* gene mutation). Of note, nonendocrine causes of primary adrenal insufficiency include infections (tuberculosis, human immunodeficiency virus, cytomegalovirus) and medications (ketoconazole, etomidate). Common causes of secondary adrenal insufficiency include hypopituitarism, central nervous system malformations, tumors, irradiation, trauma, and withdrawal from glucocorticoid therapy. (5)

Management

Acute management of an adrenal crisis includes fluid and salt replacement with isotonic, dextrose-containing fluids and initiation of stress-dose hydrocortisone. Patients should receive a single bolus of intramuscular or intravenous hydrocortisone 100 mg/m², followed by 100 mg/m² per day. Once patients improve clinically, they can be weaned down to triple-dose hydrocortisone (30 mg/m² per day) and started on fludrocortisone (0.05–0.2 mg daily). Stress-dose hydrocortisone has adequate mineralocorticoid activity; however, triple-dose hydrocortisone does not, so fludrocortisone therapy should be initiated. Long-term maintenance therapy once the patient is back at baseline status consists of hydrocortisone (8–10 mg/m² per day) and fludrocortisone.

Of note, longer-acting glucocorticoids (dexamethasone, prednisone) can be used for maintenance therapy in adults; however, they are rarely used in children because of concerns of cushingoid adverse effects and reduced final height. (1)(5)(7) Adherence and disease activity are monitored by growth velocity, skin hyperpigmentation, and electrolyte, corticotropin, and renin levels. Secondary adrenal insufficiency can be solely treated with hydrocortisone because mineralocorticoid activity remains intact, and these patients, thus, do not require fludrocortisone supplementation.

Lessons for the Clinician

- Infants presenting with vomiting, hyponatremia, and failure to thrive should raise high clinical suspicion for primary adrenal insufficiency, particularly in the context of multiple medical visits.
- Differential diagnosis of primary adrenal insufficiency includes congenital adrenal hypoplasia, congenital adrenal hyperplasia, Addison disease, adrenoleukodystrophy, autoimmune polyglandular syndrome, infections, and medications.
- Hyperpigmentation is often seen in primary but not secondary adrenal insufficiency and is the result of the stimulant effect of elevated corticotropin levels in melanocytes because corticotropin is part of the melanocortin molecule.
- Early diagnosis and treatment with fluid replacement and stress-dose hydrocortisone are imperative.
- Hypogonadotropic hypogonadism is commonly associated with congenital adrenal hypoplasia and results from mutations in the *NROB1* gene. (4) Patients can present with cryptorchidism, delayed or arrested puberty, and infertility. (2)
- A positive family history consistent with X-linked inheritance is likely to reveal a pathogenic variant in *NROB1* in almost 100% of affected individuals. (2)

References for this article are at <http://pedsinreview.aappublications.org/content/40/8/425>.

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Seema Jain and Lefkothea P. Karaviti

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2 A 10-year-old Boy Who Refuses to Walk

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PRESENTATION

A 10-year-old boy with a history of anomalous left coronary artery repaired during infancy presents to the hospital due to worsening right lower extremity pain for the past 3 weeks. The patient had residual mitral valve prolapse and moderate mitral valve regurgitation, moderate pulmonic regurgitation, and left atrial dilatation after the initial repair of his congenital heart disease. At the start of his symptoms, he was able to walk and run, but in the past few days, the pain has worsened. He now refuses to run and tries to walk slowly only when prompted to walk. His mother is also concerned that he has lost weight since the start of the pain, with accompanying anorexia. The family denies any history of trauma. He takes aspirin daily due to a history of congenital heart disease. Three weeks ago, before the pain started, his mother brought him to the hospital for evaluation of a fever. He was diagnosed as having a viral infection and was discharged. Since then his mother recalls intermittent episodes when he felt warm but on checking his temperature, it was normal.

During his evaluation in the emergency department this time, he is noted to have a temperature of 102.8°F (39.3°C) and tachycardia to 125 beats/min. Laboratory values are significant for elevated erythrocyte sedimentation rate and C-reactive protein level, a normal white blood cell count but with a neutrophilic predominance, and anemia (hemoglobin level, 9.3 g/dL [93 g/L]). An imaging study, suggested by an orthopedic surgery colleague, reveals the diagnosis.

DISCUSSION

A magnetic resonance image of the boy's lower extremity was concerning for an arterial thrombosis in the right lower extremity (Fig 1). He was admitted to the general pediatric service for further evaluation. On admission, his physical examination was significant for a child who was lying in bed in no acute distress but did not engage with discussion. Cardiac examination revealed a loud grade 6/6 systolic murmur heard best at the apex. His lower extremities were of the same size, and no overlying erythema or edema was observed. However, he had significant pain to palpation of the right posterior distal lower extremity. No palpable cord was noted, but the dorsalis pedis pulse was 1+ compared with 2+ on the contralateral lower extremity. Because of his clinical history and examination concerning for an embolic phenomenon, endocarditis was suspected. Blood cultures were obtained, and broad spectrum antibiotic drug therapy was initiated.

AUTHOR DISCLOSURE Drs Evangelista, Khetan, and Omoruyi have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Postcontrast T1-weighted magnetic resonance image of the bilateral tibia and fibula depicting a 2-cm arterial occlusion (green arrow) of the right tibioperoneal trunk. Note the change in signal from bright to dark back to bright correlating to obstruction and then reconstitution of flow.

The patient's blood cultures grew α -hemolytic *Streptococcus* within 24 hours. A 2-dimensional echocardiogram showed vegetations on the mitral valve, with partial rupture (Fig 2). Magnetic resonance imaging of the brain and foot showed evidence of septic emboli, and ophthalmologic examination revealed "cotton wool" spots and areas concerning for septic emboli. Based on these findings, the patient was treated with intravenous penicillin for 6 weeks and gentamicin for the first 2 weeks. An echocardiogram before completion of treatment showed that the vegetation

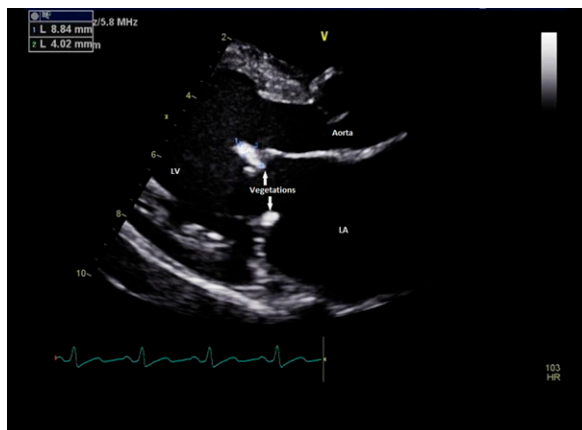


Figure 2. Echocardiogram showing vegetations attached to the mitral valve. LA=left atrium; LV=left ventricle.

on the anterior mitral valve leaflet was slightly increased in size and now pedunculated, making the risk of embolization greater. Therefore, antibiotic drug therapy was extended for an additional 2 weeks to complete a total of 8 weeks. With the extension in therapy, the size of the vegetation decreased and the patient remained stable.

Four weeks after hospital discharge, the patient was admitted for elective posterior mitral valve annuloplasty and anterior mitral valve leaflet vegetation removal. He tolerated the procedure well and was discharged. However, subsequent echocardiograms over the following 3 months showed recurrence of mitral valve regurgitation; therefore, the patient underwent a full mitral valve repair 3 months later. The patient tolerated that procedure well and was discharged in stable condition. Subsequent follow-up in the outpatient clinic has continued, and the patient remains stable.

The Condition

Bacterial endocarditis is an infection of the endothelial surface of the heart. Across 37 US children's hospitals, a little more than 1,000 children were admitted for infective endocarditis, and 68% of these patients had underlying congenital heart disease. (1) Children with congenital heart disease are at higher risk for endocarditis than the general pediatric population. Flow in a damaged valve leads to turbulence, which, in turn, damages the endothelium, resulting in formation of a thrombotic endocardial lesion. This thrombotic lesion is susceptible to becoming a nidus of infection during a transient bacteremia, and the turbulent blood flow through the damaged valve results in embolization to almost any part of the body.

The clinical hallmarks of endocarditis include bacteremia, cardiac invasion by microbes, and peripheral embolization. Pediatric endocarditis is further classified into subacute and acute processes. The subacute process is hallmarked by a protracted clinical course of low-grade fever, general malaise, sweating, and weight loss. Patients with acute endocarditis have a rapid illness, high fever, and very ill appearance. The most common organisms associated with pediatric endocarditis include *Staphylococcus* and *Streptococcus* species. (2) However, *Staphylococcus aureus* is the most common causative pathogen and is associated with the highest mortality rate seen in acute endocarditis especially related to systemic emboli. (2)

Most commonly, the diagnosis of endocarditis is made by following the revised Duke criteria (Table 1). (2)(3) The revised Duke criteria require the presence of 1 of 2 pathologic criteria or certain combinations of clinical results divided into major and minor findings. (2)(3) The pathologic

TABLE 1. Revised Duke Criteria for the Diagnosis of Endocarditis

| MAJOR DIAGNOSTIC CRITERIA | MINOR DIAGNOSTIC CRITERIA |
|---|--|
| Positive blood culture for typical infective endocarditis organisms from 2 separate blood cultures or 2 positive cultures from samples drawn >12 h apart, or 3 or a majority of 4 separate cultures of blood (first and last sample drawn 1 h apart) | Predisposing heart condition |
| Echocardiogram with oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomical explanation, or abscess, or new partial dehiscence of prosthetic valve or new valvular regurgitation | Temperature >100.4°F (>38°C) |
| Single positive blood culture for <i>Coxiella burnetii</i> or anti-phase 1 immunoglobulin G antibody titer >1:800 | Vascular phenomena: arterial emboli, pulmonary infarcts, mycotic aneurysms, intracranial bleed, conjunctival hemorrhages, Janeway lesions Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor Microbiologic evidence: positive blood culture but does not meet a major criterion or serologic evidence of active infection with organism consistent with endocarditis (excluding coagulase-negative <i>Aggregatibacter</i> staph, and other common contaminants) |

criteria include direct evidence of endocarditis based on histologic findings and positive Gram-stain or culture of specimens obtained from surgery or autopsy. The clinical diagnosis requires the presence of 2 major and 0 minor criteria, 1 major and 3 minor criteria, or 0 major and 5 minor criteria.

Embolization, a known complication of bacterial endocarditis, has been described in 11% to 44% of patients, and one-third of these patients have embolization to the peripheral vasculature. (4) As was seen in our patient, large (>10 mm), left-sided, and pedunculated vegetations are more likely to embolize. (4) Complications of embolization to the peripheral vasculature typically present with worsening pain at the site and fever.

Differential Diagnosis

In a child who presents with leg pain, the differential diagnosis can be broad and includes fracture due to accidental or nonaccidental trauma, musculoskeletal strain/sprain, infection, myositis, malignancy, embolic phenomenon, and thrombosis.

Treatment

The management of bacterial endocarditis is highly dependent on the underlying causative microbial agent. Therefore, it is extremely important to obtain blood cultures when the diagnosis is in question so that empirical therapy may be initiated and then tailored based on several factors, including the causative agent, previous antibiotic exposure, route

of infection, whether the infected valve is native or prosthetic, and whether the infectious process is subacute or acute. (5) In many cases, consultation with an infectious disease specialist is recommended.

Treatment of endocarditis requires the use of antibiotic agents specifically targeting bacterial pathogens (Table 2) and generally requires inpatient treatment. Culture-negative endocarditis occurs rarely in children and is usually diagnosed only when there is clinical or echocardiographic evidence and suspicion of bacterial endocarditis but persistently negative blood cultures. (5)

During antibiotic drug treatment, the patient's clinical course should be monitored with antimicrobial levels, echocardiography, and repeated blood cultures. If a patient is receiving gentamicin or vancomycin, levels of these antimicrobial agents should be checked at least once each week. (5) Repeated echocardiography may be needed to assess for changes in vegetations and to evaluate valvular and myocardial function. (3)(6) Furthermore, repeated blood cultures may be needed to demonstrate eradication of the causative agent and if symptoms recur.

In patients who fail medical therapy and who continue to have persistent vegetations despite antibiotic drug therapy, surgical intervention may be considered. The most common reasons for surgical intervention are congestive heart failure, progressive valvular dysfunction, and embolic phenomena. (3)(5)

When bacterial endocarditis is recognized and treated early, patients typically do well. However, the overall

TABLE 2. Antibiotic Regimens for the Treatment of Endocarditis Based on Causative Organism (4)

| CAUSATIVE AGENT | ANTIBIOTIC REGIMEN |
|---|---|
| Viridans group streptococci <i>Streptococcus bovis</i> | Penicillin G for 4 wk OR Ampicillin for 4 wk OR Ceftriaxone for 4 wk |
| Enterococci | Penicillin G for 4–6 wk OR Ampicillin + gentamicin for 4–6 wk OR Ceftriaxone + ampicillin for 6 wk |
| Staphylococci | Methicillin sensitive Native valve: Nafcillin/oxacillin for 4–6 wk OR Cefazolin for 4–6 wk Prosthetic valve: Nafcillin/oxacillin for 6 wk OR Cefazolin + rifampin for 6 wk + gentamicin for first 2 wk Methicillin resistant Native valve: Vancomycin for 6 wk Prosthetic valve: Vancomycin for 6 wk + rifampin for 6 wk + gentamicin for first 2 wk |
| Gram-negative organisms (HACEK [<i>Haemophilus</i> species, <i>Aggregatibacter</i> species, <i>Cardiobacterium hominis</i> , <i>Eikenella corrodens</i> , <i>Kingella</i>]) | Ceftriaxone for 4 wk OR Cefotaxime for 4 wk OR Ampicillin + gentamicin for 4 wk |

mortality rate is approximately 5%; effective and adequate treatment is key. (2) Most children with bacterial endocarditis have an identifiable risk factor such as preexisting heart disease, prematurity, or an underlying palliative shunt or prostheses. In these patients in particular, the risk of complications and the rates of morbidity and mortality are higher. Inadequate or delayed treatment, particularly, in high-risk patients, can lead to life-threatening complications such as heart failure, extension of the infection resulting in arrhythmias and heart block, or metastatic infection (such as osteomyelitis, pneumonia, or distal abscesses), as demonstrated in this patient. (2)

Lessons for the Clinician

- Bacterial endocarditis is a potentially life-threatening disease commonly seen in patients with an underlying

risk factor, such as preexisting heart disease or an indwelling catheter.

- Due to the increased survival rate of children with congenital heart disease and the increased use of central venous catheters, the incidence of bacterial endocarditis has increased during the past 3 decades.
- The clinical presentation of bacterial endocarditis is highly variable and may include nonspecific complaints such as low-grade fevers, fatigue, arthralgias, and myalgias.
- The treatment for bacterial endocarditis should be guided by the causative agent identified on blood culture, the route of infection, the cardiac history (prosthetic versus native valve), and the presentation of infection (acute versus subacute).

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2 A 13-year-old Boy with a Perplexing Rash

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AUTHOR DISCLOSURE Drs Salloum and Lane have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 13-year-old boy presents to the emergency department with a fever for 1 day and a worsening rash for 1 month. He initially took amoxicillin because the rash was thought to be due to scarlet fever. The amoxicillin was changed to azithromycin after 3 days due to concern for allergic reaction after the development of facial swelling. A week after completion of azithromycin therapy the patient was prescribed prednisone due to worsening of his rash, which became pruritic with drainage from some lesions. A review of systems is otherwise negative. The patient has no eczema, food, or drug allergies. He has no significant medical history other than a recent diagnosis of bipolar disorder for which he started taking carbamazepine 2 months before his presentation to the emergency department. He is up to date on his immunizations, without known sick contacts. Physical examination reveals an uncomfortable child in mild distress complaining of pruritus. His temperature is 102.2°F (39°C), heart rate is 134 beats/min, blood pressure is 117/69 mm Hg, respiratory rate is 20 breaths/min, and oxygen saturation is 99% on room air. He has a diffuse maculopapular erythematous rash over his torso and extremities (Fig). The rash is most concentrated on his face, neck, and upper trunk, with the flexural creases being the most involved. No oral lesions are noted, but he does have facial edema with cracked lips. Cervical and groin lymph nodes are enlarged. The rest of his examination findings are unremarkable. Laboratory evaluation reveals a white blood cell count of $23.7 \times 10^3/\mu\text{L}$ ($23.7 \times 10^9/\text{L}$), with 30% neutrophils, 9% bands, 11% lymphocytes, and 50% eosinophils. The absolute eosinophil count is $11.85 \times 10^3/\mu\text{L}$ ($11.85 \times 10^9/\text{L}$). A peripheral smear shows atypical lymphocytes. Liver tests are significant for elevated alanine aminotransferase and aspartate aminotransferase levels of 157 U/L (2.62 $\mu\text{kat/L}$) and 77 U/L (1.29 $\mu\text{kat/L}$), respectively. He has normal albumin, bilirubin, and electrolyte levels and renal function test results. A blood sample is sent for culture, and he is started on vancomycin for concern of resistant *Staphylococcus aureus* cellulitis. The constellation of history and laboratory results helps in making the final diagnosis.

DISCUSSION

Diffuse skin rash and peripheral eosinophilia raised a concern for an adverse drug reaction. Carbamazepine was a new medication for the patient, which



Figure. Skin eruption in the patient's upper extremity.

was started 1 month before the rash onset. Subsequently, the patient was diagnosed as having drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. DRESS is a rare, potentially life-threatening adverse reaction to many drugs, most commonly sulfonamides and aromatic anticonvulsants (eg, phenytoin and carbamazepine). Many other drugs have been implicated as well. The incidence of DRESS ranges from 1 in 1,000 to 1 in 10,000 drug exposures. DRESS can be more difficult to diagnose compared with other adverse drug reactions due to the presence of a longer latency period, which typically ranges from 3 to 8 weeks. There is a genetic component that predisposes HLA-A*3101-positive individuals to develop DRESS if exposed to carbamazepine. The clinical picture of DRESS is characterized by a severe skin eruption as well as potential systemic symptoms, including fever, hematologic abnormalities (eosinophilia or atypical lymphocytes), and internal organ involvement. Skin rash is the most frequently reported symptom and usually involves more than 50% of the body, with or without facial edema. The most commonly encountered skin manifestation of DRESS syndrome is an erythematous morbilliform rash, in contrast to Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which

are bullous disorders of the skin with appearance similar to burn injuries. DRESS can also be distinguished from SJS/TEN by the absence of significant mucosal involvement, as well as the presence of marked eosinophilia (eosinophil count $>700/\mu\text{L}$ ($0.7 \times 10^9/\text{L}$)). The pathogenesis of DRESS is not completely understood. Reactivation of human herpesvirus (human herpesvirus 6 and 7 and Epstein-Barr viruses) has been discussed as potentially relevant in some patients.

Diagnosis and Treatment

The European Registry for Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system is used to aid the diagnosis of DRESS through a grading system. The grading system assigns “no,” “possible,” “probable,” or “definite” based on the patient’s total score and can be found at the RegiSCAR Project website (<http://www.regiscar.org>). Early recognition and prompt removal of the offending agent is the main treatment for patients with DRESS. Topical corticosteroids and emollients are used for mild cases, and systemic corticosteroids for more severe cases. Full recovery usually takes weeks to months, even after discontinuation of the offending drug. In fact, resolution of the rash in less than 15 days makes DRESS unlikely. Mortality rates range from 5% to 10%, with severe hepatitis being responsible for most deaths.

Patient Course

Based on the RegiSCAR scoring system, our patient was found to have a “definite” case of DRESS syndrome with a score of 6 (2 points for eosinophilia [eosinophil count $>1,500/\mu\text{L}$ ($1.5 \times 10^9/\text{L}$)], 1 point for enlarged lymph nodes, 1 point for atypical lymphocytes, 1 point for rash involving more than 50% of his body, and 1 point for liver involvement). The patient’s kidney function remained normal, as did his creatine kinase and lipase levels. He had normal echocardiographic findings and a normal troponin level, and he did not develop respiratory symptoms. Titers and polymerase chain reaction DNA for cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6 were obtained on 2 occasions, 3 weeks apart, and were negative for evidence of viral reactivation in this case. The patient was taking carbamazepine and amoxicillin, which are 2 drugs associated with DRESS syndrome. However, carbamazepine was thought to be the offending drug in this case based on the time frame of the rash presentation and was discontinued on hospital admission. Of note, carbamazepine can also cause SJS and TEN. The patient was started on intravenous methylprednisolone, 2 mg/kg per day, which was weaned later

to oral corticosteroids. Fluids and electrolytes were monitored closely. His blood culture ultimately grew *S aureus*, likely secondary to his extensive skin inflammation, for which he was treated with vancomycin based on sensitivities of the laboratory for the *Staphylococcus* species. He was discharged after 10 days of hospital stay on a prolonged oral corticosteroid taper. The patient was advised to avoid carbamazepine in the future and was monitored through follow-up care. The rash took 4 months to resolve.

Lessons for the Clinician

- Obtaining a detailed history in patients with prolonged, worsening rash provides insight into potential causative agents.
- Maintain a high index of suspicion for drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome

in patients who develop skin eruption with eosinophilia 3 to 8 weeks after starting a new drug.

- DRESS syndrome is distinguished from SJS/TEN by morbilliform rash, absence of significant mucosal involvement, and the presence of marked peripheral eosinophilia.
- Immediate withdrawal of the offending drug with continued avoidance in the future is the mainstay of treatment in DRESS syndrome as well as systemic corticosteroids in severe cases. Full recovery typically takes weeks to months.
- Recognizing this syndrome is important as the mortality rate can be up to 10%.

Suggested Readings for this article are at <http://pedsinreview.aappublications.org/content/40/2/82>.

Case 2: A 13-year-old Boy with a Perplexing Rash

Shafee Salloum and Aphton Lane

Pediatrics in Review 2019;40;82

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2 Lethargy and Ataxia in a 3-year-old Girl

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PRESENTATION

A 3-year-old previously healthy girl presents with progressive lethargy and ataxia over the past 7 days. Her mother reports that she has been increasingly sleepy and difficult to awaken, and over the past 3 days has had increasingly unsteady gait. In addition, she has had fatigue, cough, and decreased oral intake for the past 2 to 3 weeks. Her mother denies any fevers, weight loss, travel, or unusual exposures. She and her family are from an urban area in the Southeastern United States.

On physical examination she is afebrile without tachypnea or tachycardia. She is ill-appearing and sleepy but arouses with stimulation and follows simple commands. She has right-sided ptosis, right-sided facial weakness, and right-sided arm and leg weakness. Deep tendon reflexes are present in all extremities. Cerebrospinal fluid (CSF) analysis shows a white blood cell count of $68/\mu\text{L}$ ($0.07 \times 10^9/\text{L}$) with 33% neutrophils, 60% lymphocytes, and 7% monocytes; a red blood cell count of $42/\mu\text{L}$ ($0.00042 \times 10^{12}/\text{L}$); a glucose level of 26 mg/dL (1.4 mmol/L); and a protein level of 115 mg/dL (1.15 g/L). The remainder of the physical examination and basic laboratory values, including serum electrolytes, renal and liver function, and complete blood cell count, are within normal limits, although the C-reactive protein level is elevated at 10.8 mg/L (102.9 nmol/L) (reference range, <9.0 mg/L [<85.7 nmol/L]).

A computed tomographic (CT) scan of the head shows tetraventricular hydrocephalus (Fig 1). Empirical ceftriaxone, vancomycin, doxycycline, and acyclovir are started, without any clinical improvement. A brain magnetic resonance image demonstrates basilar meningitis. Results of CSF testing with bacterial culture, fungal culture, acid-fast bacilli (AFB) stain and culture, and herpes simplex virus polymerase chain reaction are negative. Results of additional evaluations with tuberculosis (TB) skin testing, blood culture, Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus testing are negative. Chest radiography reveals left upper lobe atelectasis. Despite a negative exposure history, negative TB skin test result, and inconclusive initial chest radiograph, empirical therapy for TB was started on day 2 of hospitalization due to clinical deterioration. Chest CT (Fig 2) leads to additional testing that reveals the diagnosis.

AUTHOR DISCLOSURE Drs Gavigan, Hysmith, and Bagga have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

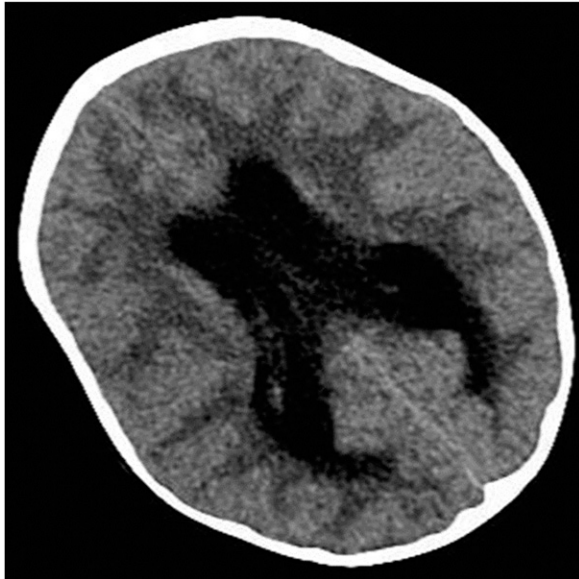


Figure 1. Computed tomographic scan of the head of the patient demonstrating tetra-ventricular hydrocephalus.

DISCUSSION

Clinical Course

On further history, the mother revealed that the patient's aunt was treated for active TB approximately 1 year earlier and had been noncompliant with her medications. In addition, whereas the patient's siblings had received prophylactic therapy at that time, the patient had not. Given the subtle chest radiography findings, a chest CT scan was obtained, and it demonstrated a cavitory lesion in the left upper lobe. Subsequent gastric aspirate culture was positive for *Mycobacterium tuberculosis*, confirming the diagnosis of TB.

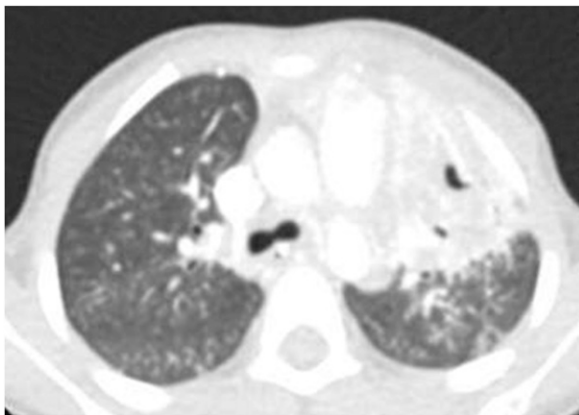


Figure 2. Computed tomographic scan of the chest of the patient demonstrating a left upper lobe cavitory lesion.

After starting rifampin, isoniazid, pyrazinamide, moxifloxacin, and prednisone for TB meningitis, she began to demonstrate clinical improvement. Her mental status and neurologic examination findings improved; however, she did require intensive rehabilitation, as well as a ventriculo-peritoneal shunt due to persistent hydrocephalus. She was eventually discharged to finish her course of medication through direct observed therapy by the health department.

Epidemiology and Pathogenesis

Central nervous system (CNS) involvement of TB is rare, occurring in less than 2% of cases, with meningitis representing approximately 1%. However, it is most common in children, especially those younger than 2 years. (1) Although the overall annual rates of TB in the United States have decreased to approximately 3 per 100,000, the morbidity and mortality associated with TB meningitis remain high. (1)(2) Involvement of the CNS results from direct extension and establishment of infection in the brain and meninges during periods of bacilemia that occur with primary infection or late reactivation. Small caseating granulomas form in the brain tissue, and meningitis occurs when these granulomas rupture, releasing bacteria into the subarachnoid or ventricular spaces. (1)(3)

Clinical Presentation

Patients with TB meningitis can present with any number of nonspecific symptoms but typically develop a subacute clinical course that progresses through 3 stages. Stage I typically lasts 1 to 3 weeks and consists of an initial prodromal phase of malaise, headache, and low-grade fever. Patients in stage I of the disease have no neurologic deficits or hydrocephalus. Stage II is characterized by meningeal inflammation and cranial nerve palsies. These patients often have focal neurologic deficits, severe headaches, vomiting, lethargy, and confusion. The exact duration of stage II is unclear and is determined by the underlying host immunity and the disease burden. Finally, stage III involves worsening mental status, with stupor, coma, seizures, and hemiparesis, due to progressive hydrocephalus and vasculitis. (1)(2)(3) Weight loss and night sweats, frequently seen in patients with pulmonary TB, are present in only 25% of patients with TB meningitis. Prognosis is often directly related to early initiation of anti-TB therapy. Unfortunately, as many as 90% of children with TB meningitis are not identified until stage II or III, when they develop focal neurologic signs. (2)(4)

Diagnosis

Definitive diagnosis is established by AFB stain and culture of CSF, but this is challenging given the low sensitivity of

CSF AFB stain and culture. (2)(4) Similarly, TB skin testing and interferon- γ release assays are unreliable in the diagnosis of CNS TB, and they are positive in only 33% of cases. (1)(2)(4) Nucleic acid amplification tests on CSF are not readily available and are limited by their varying sensitivity and specificity. (5)

With no reliable test available for TB meningitis, clinicians must rely on history and clinical, laboratory, and radiographic findings. In a young child, TB meningitis is a consequence of primary infection and, thus, requires exposure to active TB. Accordingly, a history of any patient exposure to confirmed or potential TB cases is important. However, a contact case is identified in only 50% to 70% of patients with TB meningitis, and there is often a significant delay in identifying this source. Abnormalities in CSF are one of the most consistent findings in patients with TB meningitis. The characteristic lymphocytic pleocytosis with extremely elevated protein and decreased glucose levels is seen in approximately 80% of patients. Imaging to look for pulmonary disease and evaluate for CNS disease is also valuable in making the diagnosis. The most common radiographic findings of TB meningitis include abnormal chest radiographs (90% of patients) and hydrocephalus (80% of patients). (1)(4) Less commonly, basilar meningitis and infarcts are seen on head imaging. (1)(2)(4)

Management

Anti-TB therapy typically consists of rifampin, isoniazid, pyrazinamide, and ethambutol. (1)(3) In cases of meningitis, an aminoglycoside, ethionamide, or moxifloxacin should be substituted for ethambutol given their superior CSF penetration. (5)(6) Treatment with anti-TB therapy is recommended for 9 to 12 months. The 4 medications are

administered for the first 2 months, and then treatment is completed with rifampin and isoniazid for an additional 7 to 10 months. In addition to antimicrobials, corticosteroids are also recommended for 4 to 6 weeks, followed by a taper. (1) (5) Corticosteroids have been associated with decreased mortality and neurologic sequelae; however, ventriculoperitoneal shunting is frequently required to relieve hydrocephalus.

Lessons for the Clinician

- Nonspecific symptoms, rarity of occurrence, and difficulties with history can lead to delays in diagnosis and initiation of appropriate therapy in patients with tuberculosis (TB) meningitis.
- TB should be suspected in patients with subacute aseptic meningitis even in the absence of typical risk factors (travel to or residence in an endemic country, known exposure, weight loss, chronic cough).
- Cerebrospinal fluid (CSF) culture for *Mycobacterium tuberculosis* and TB skin testing are often unreliable for diagnosis of TB meningitis owing to poor sensitivity.
- TB meningitis is most commonly associated with lymphocytic pleocytosis, an elevated protein level, and a low glucose level on CSF analysis and with hydrocephalus on head imaging.
- In individuals with suspected TB meningitis, empirical TB therapy should be initiated, even in the absence of definitive diagnosis, to reduce morbidity and mortality associated with the disease.
- An attempt should be made to find the primary pulmonary focus in children with suspected extrapulmonary TB.

References for this article are at <http://pedsinreview.aappublications.org/content/40/4/194>.

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2 16-year-old Boy with Intractable Nausea and Vomiting

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PRESENTATION

A 16-year-old boy with a medical history of mild intermittent asthma presents to the emergency department with a 4-day history of achy, 8/10 epigastric and periumbilical abdominal pain with intractable nonbilious, nonbloody emesis. He has presented with similar episodes 3 times previously at another hospital, without a definitive diagnosis being made. He also has new-onset chest pain (6/10) since the morning of presentation that radiates to his back. This pain is associated with neck swelling and “air pockets” under the skin. He states that such air pockets have occurred previously with episodes of prolonged emesis. He denies diarrhea and has been afebrile. He states that hot showers improve his abdominal pain and emesis; he often showers up to 10 times a day. He has been taking omeprazole for presumed gastritis diagnosed 1.5 months ago at an outside hospital, but he takes no other medications. He acknowledges a history of frequent marijuana use.

Vital signs are significant only for a heart rate of 114 beats/min. He appears to be in mild distress. Findings from cardiovascular and respiratory examinations are normal other than tachycardia. Scleral icterus and mild jaundice are noted. Marked, diffuse subcutaneous emphysema is palpated from his anterior chest to right neck and lateral face. The abdomen is soft, nontender, and nondistended, with normoactive bowel sounds and no appreciable masses. His neurologic examination findings are normal, including strength, sensation, and reflexes of the upper and lower extremities. Laboratory results are remarkable for an elevated white blood cell count (14,500/ μ L [14.5×10^9 /L]), hyponatremia (sodium level, 129 mEq/L [129 mmol/L]), and hypochloremia (chloride level, 91 mEq/L [91 mmol/L]). Lipase, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels are normal. A chest radiograph is obtained (Fig 1).

DISCUSSION AND DIAGNOSIS

Kidney, ureter, and bladder radiography is ordered to rule out free air associated with the patient's abdominal pain and emesis. It displays a normal bowel gas pattern. The persistent nausea and vomiting are thought most likely to be due to cannabinoid hyperemesis syndrome (CHS); this is supported by his history of

AUTHOR DISCLOSURE Ms Kelly and Dr Van Opstal have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

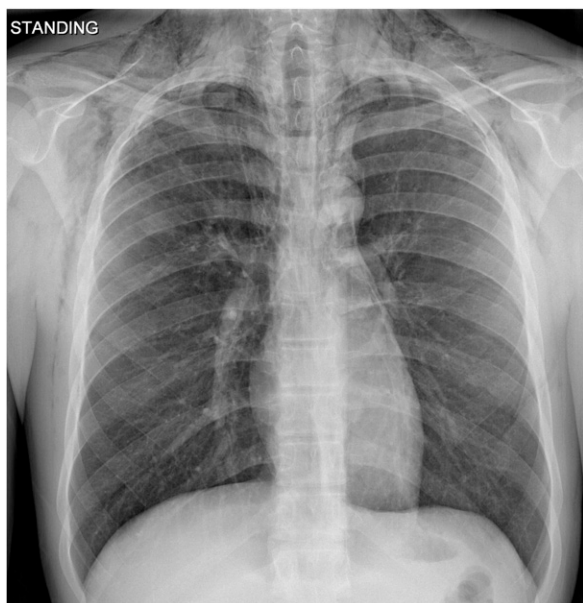


Figure 1. A chest radiograph the day of admission demonstrates subcutaneous emphysema.

relief from hot showers. He undergoes subsequent upper endoscopy, which shows only mild gastritis.

A chest radiograph confirms the presence of extensive subcutaneous emphysema, as well as possible pneumomediastinum. No evidence of a pneumothorax is found. A computed tomography angiogram of the chest confirms extensive subcutaneous emphysema, as well as pneumomediastinum and pneumorrhachis (Fig 2). Pediatric surgery is concerned for esophageal perforation as the etiology for the subcutaneous emphysema, so they recommend an esophagogram. It is negative for esophageal leak or perforation. The pneumomediastinum is thought to be a spontaneous result of excessive emesis. Neurosurgery is consulted



Figure 2. A computed tomographic scan of the chest with intravenous contrast on the day of admission demonstrates extensive subcutaneous emphysema, pneumomediastinum, and pneumorrhachis.

for his pneumorrhachis. Computed tomography of the spine shows extensive involvement; however, neurologic examination is normal, and the patient is completely asymptomatic.

Case reports and presentations of CHS are well documented in the adult literature. However, because it is a clinical diagnosis without laboratory or radiographic screening tests, misdiagnosis is common. (1) Typically, patients present with abdominal pain, nausea, and recurrent emesis in the context of a significant history of cannabis use. The syndrome is commonly described as having 3 distinct phases. During the prodromal phase, which, if present, lasts anywhere from a few months to a few years, the patient experiences early-morning nausea and a fear of vomiting, but maintains a normal appetite and may continue or increase cannabis use. The hyperemetic phase follows and involves intense, cyclic vomiting episodes lasting 24 hours to several days. The patient will classically relieve these episodes with hot showers. This phase of the syndrome is typically when patients report to the emergency department for rehydration; evaluation is usually normal. The final recovery phase begins only once the patient ceases cannabis consumption. Relief usually occurs within a week. (1)(2)

The definitive treatment of CHS is cessation of cannabis use. During the hyperemesis phase, rehydration with intravenous fluids and supportive care are the cornerstones of management. Dehydration due to intractable vomiting and frequent, prolonged hot showers is common in patients with CHS; case reports of acute kidney injury in adults with CHS reinforce how important rehydration with kidney function monitoring is during treatment of CHS. (3) Standard antiemetic agents, such as ondansetron, generally do not provide symptomatic relief of nausea and vomiting. (1) Some preliminary case reports regarding the effectiveness of topical capsaicin cream at relieving abdominal pain and vomiting in both adult and pediatric populations with CHS are promising. (4) Counseling on cannabis cessation with outpatient follow-up is suggested to prevent recurrence of CHS.

Although spontaneous pneumomediastinum (Hamman syndrome) is a well-documented adverse effect of intractable vomiting, the literature does not specifically cite CHS as a precipitating etiology. Other commonly cited causes of pneumomediastinum include coughing, Valsalva maneuver, bronchial asthma, and deep sea diving. (5) In this condition, alveoli become overdistended to the point of rupture, releasing free air that diffuses to the mediastinum. (5)(6) Incidence overall in pediatric populations is 1 in 8,000 to 1 in 15,000. (7) Clinically, pneumomediastinum

in children most commonly presents as chest or neck pain, but it can also include sore throat, cough, dyspnea, or pain that radiates to the back. Chest radiography is diagnostic in most cases, and follow-up can usually be performed clinically, without the need for further studies. (7) A 2016 retrospective study revealed that all esophagrams performed in the setting of spontaneous pneumomediastinum to evaluate for the presence of esophageal rupture were negative, and, therefore, some experts do not think that they are indicated. (8) Treatment is mostly supportive and must address the underlying cause of the pneumomediastinum. (7)(9)

Pneumorrhachis, in which air from ruptured alveoli enters the spinal cord at either the epidural or subdural level, is an extremely rare condition, especially as a complication of pneumomediastinum. Documented cases indicate that spinal trauma and epidural placement are the most common cause of spontaneous, isolated, pneumorrhachis, although violent vomiting, abscesses, asthma, and coughing can precipitate this condition. (5)(10) In the case of pneumorrhachis after pneumomediastinum, free air from the mediastinum travels to the fascia of the neck, at which point it crosses the neural foramen to the epidural space. (5) Computed tomography of the spine is the most reliable diagnostic tool. In most cases, patients are asymptomatic, although neurologic deficits have been documented in a few cases, and meningitis is a rare possible adverse effect. (6)(10) Conservative management for asymptomatic patients

is supportive, with attention given to any underlying conditions. Needle decompression, dexamethasone, and hyperbaric oxygen treatment are nonsurgical treatment options previously documented for use in refractory or symptomatic cases. (10)(11)

Our patient, unfortunately, did not quit using marijuana and had frequent subsequent emergency department visits and hospitalizations. He did not have further incidents of pneumomediastinum or pneumorrhachis.

Adolescents' access to marijuana continues to increase as more states legalize its use, necessitating that clinicians screen for use during routine health maintenance intakes and keep a high index of suspicion for CHS among those who present with cyclic vomiting (4).

Lessons for the Clinician

- In pediatric patients with intractable nausea and vomiting without relief from classic therapies, maintain a high index of suspicion for cannabis hyperemesis syndrome, especially in those who endorse a history of marijuana use.
- Although emerging studies suggest that topical capsaicin cream may help relieve nausea and vomiting in patients with CHS, the only definitive treatment is cessation of marijuana use.

References for this article are at <http://pedsinreview.aappublications.org/content/40/6/305>.

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Index of Suspicion

2 Acute Onset and Worsening of Anemia in a 3-year-old Boy

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PRESENTATION

A 3-year-old boy of Persian descent presents to his primary care physician with 2 days of fever to a temperature of 101.8°F (38.8°C) and a 1-day history of jaundice. A review of systems reveals that he has decreased oral intake, headache, looser stools that are orange in color, and 3 recent episodes of nonbloody, nonbilious vomiting. At the visit he has bright red urination. The patient has a brother who was treated for streptococcal pharyngitis 1.5 weeks ago. His medical history is not significant for any previous illnesses. His birth history reveals that the patient was jaundiced but did not require any phototherapy. His family history does not reveal any kidney or hematologic abnormalities except for a brother who required phototherapy at birth.

Results of abdominal ultrasonography and chest radiography are normal. The patient is admitted to the hospital with a heart rate of 98 beats/min, a blood pressure of 108/73 mm Hg, a respiratory rate of 22 breaths/min, and a temperature of 97.5°F (36.4°C). On physical examination the patient appears tired and is noted to have jaundice with mild scleral icterus. His oropharynx is clear, with mildly erythematous tonsils but no exudates, and he has serous fluid behind the right tympanic membrane. The patient has no rash, no palpable hepatosplenomegaly, and no cervical, axillary, or inguinal lymphadenopathy.

Initial laboratory tests show urine analysis with brown color, a glucose level of 250 mg/dL (13.9 mmol/L), large blood cells, ketone levels of 40 mg/dL, a protein level greater than 0.3 g/dL (>3 g/L), a urobilinogen level greater than 8.0 mg/dL (0.44 mmol/L), a moderate bilirubin level, moderate leukocyte esterase, positive nitrite, 0.2 white blood cells per high-power field, 6 to 10 red blood cells per high-power field, moderate bacteria, occasional squamous epithelial cells, and many amorphous crystals. The serum electrolytes and creatinine level are within normal limits. The alanine aminotransferase level is 27 U/L (0.45 μ kat/L), aspartate aminotransferase level is 178 U/L (2.97 μ kat/L), alkaline phosphatase level is 245 U/L (4.09 μ kat/L), and total bilirubin level is 4.9 mg/dL (83.8 μ mol/L).

A complete blood cell (CBC) count shows a white blood cell count of 14,400/ μ L (14.4×10^9 /L), a hemoglobin level of 8.3 g/dL (83 g/L), a hematocrit value of 23.4%, and a normal concentration of platelets. His mean corpuscular volume is 74 fL, which is the lower end of normal for his age. His red blood cell

AUTHOR DISCLOSURE Drs Khera, Hafeez, and Padilla have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

distribution width is 14.4 fL, which is the upper limit of normal for his age. He has normal mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration. Other tests included a rapid mononucleosis assay, a hepatitis B surface antigen, and a hepatitis C antibody, which are negative, and an antistreptolysin O titer, which is normal. The γ -glutamyltransferase level is less than 3 U/L ($<0.05 \mu\text{kat/L}$), and coagulation studies show a prothrombin time of 14.7 seconds, an international normalized ratio of 1.13, and a partial thromboplastin time of 28.6 seconds. Rapid influenza nasopharyngeal and streptococcal throat swabs are both negative.

The patient has 2 voids with black-colored urine 4 hours after admission. A repeated CBC count shows that the hemoglobin level has decreased to 6.0 g/dL (60 g/L) and the hematocrit level has decreased to 16.9%. Additional laboratory tests show a lactate dehydrogenase level of 2,936 U/L ($49.0 \mu\text{kat/L}$), a significantly decreased haptoglobin level of less than 8 mg/dL ($<80 \text{ mg/L}$), and a total bilirubin level of 3.3 mg/dL ($56.4 \mu\text{mol/L}$), with a 0.3 mg/dL ($5.1 \mu\text{mol/L}$) direct component. The reticulocyte count is mildly elevated at 1.8%, the C3 level is slightly decreased at 84 mg/dL, and the immunoglobulin (Ig) A level is 95 mg/dL (950 mg/L). Further testing reveals the diagnosis for this patient.

DISCUSSION

Hemolytic anemias are diagnosed in anemic patients who have an elevated reticulocyte count, indicating an appropriate bone marrow response. These patients commonly have elevated intracellular markers, such as bilirubin and lactate dehydrogenase, and decreased haptoglobin levels. Hemolytic anemia has multiple causes and variable presentations.

Hemolytic anemias can be either cellular or extracellular. Cellular diagnoses are due to pathology with the red blood cell membrane, enzymes, or hemoglobin. Extracellular diagnoses indicate a pathology that destroys the red blood cell externally, such as antibodies, mechanical factors, or plasma factors. Most cellular defects are inherited, and most extracellular defects are acquired. (1)

This patient is unlikely to have a cellular defect, especially because he has not had any previous episodes of hemolysis, his normal newborn screen rules out sickle cell disease, and his family history is negative for inherited cellular defects. Most red blood cell membrane defects would result in abnormally shaped red blood cells on a peripheral smear, such as spherocytes or elliptocytes,

which can also result in splenomegaly. None of these were identified in our patient.

Etiologies for extracellular defects include autoimmune disorders or fragmentation due to direct damage to the red blood cell membrane. In addition, plasma factors, such as liver disease, abetalipoproteinemia, vitamin E deficiency, and Wilson disease, may cause extracellular hemolytic anemia. These plasma factors make red blood cells more susceptible to oxidative damage. Fragmentation can also occur due to infections that would lead to disseminated intravascular coagulation or hemolytic uremic syndrome. (1) The patient has a slightly elevated aspartate aminotransferase level but no other liver enzyme elevation that would indicate liver disease or concern for Wilson disease. The physical examination findings also did not reveal Kayser-Fleischer rings or any growth, vision, or balance problems, making abetalipoproteinemia or vitamin E deficiency less likely.

Furthermore, hemolytic anemias can also be classified by extravascular or intravascular hemolysis (Fig). In intravascular hemolysis, the red blood cell is damaged while in circulation, releasing hemoglobin. Examples of intravascular hemolysis are mechanical trauma (which can occur from prosthetic valves), complement fixation, or other toxic damage to the red blood cell. Free hemoglobin binds to circulating haptoglobin and is degraded and cleared by the liver. When haptoglobin becomes saturated by hemoglobin, unbound free hemoglobin is then excreted by the kidneys.

In contrast, extravascular hemolysis occurs when macrophages in the liver or the spleen engulf the red blood cell due to abnormalities with the red blood cell itself. Patients with exclusive extravascular hemolysis likely do not have red urine because all the hemoglobin then circulates through the liver. Our patient's presentation is most consistent with intravascular hemolysis due to the presence of hematuria and the lack of hepatosplenomegaly.

The Condition

Autoimmune hemolytic anemia (AHA) can occur intravascularly or extravascularly. Autoimmune etiology is determined by the direct antiglobulin test (DAT) or the Coombs test. The Coombs test result returned positive for our patient. The DAT IgG result returned negative but the DAT C3 result returned positive, which helps guide future therapy. The DAT can detect either IgG, indicating warm AHA, or fragments of complement, mainly C3, indicating cold agglutinin syndrome. Approximately 80% of AHAs are diagnosed as the warm antibody type. In cold antibody agglutinin syndrome, only complement is detected due to

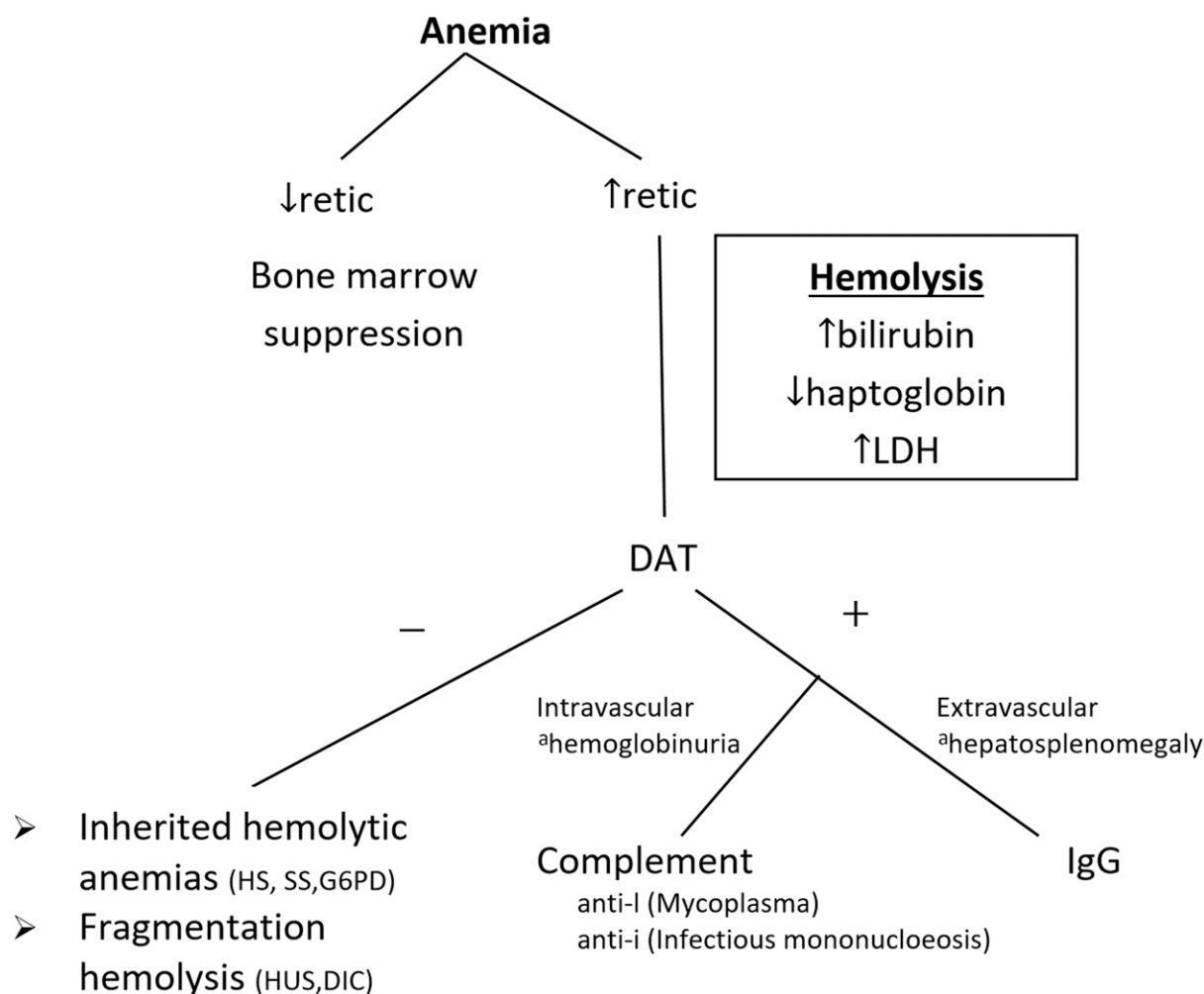


Figure. A basic approach to different hemolytic anemia diagnoses. DIC=disseminated intravascular coagulation, G6PD=glucose-6-phosphate dehydrogenase deficiency, HS=hereditary spherocytosis, HUS=hemolytic uremic syndrome, IgG=immunoglobulin G, LDH=lactate dehydrogenase, retic=reticulocyte count, SS=sickle cell anemia. ^a Commonly associated objective findings.

dissociation of antibody during washing of red blood cells. Complement fixation occurs intravascularly, causing hemoglobinuria or red-colored urine. Hemoglobinuria is most often seen in cold agglutinin syndrome but also can be seen with some drug-induced immune hemolytic anemias, often caused by cephalosporins. (2)

Cold agglutinin syndrome can further be classified by the type of antigen that is involved: I or i. Anti-I is mostly seen in patients who have an infection with antibody-positive *Mycoplasma pneumoniae*, and anti-i is mostly seen in patients with acute infectious mononucleosis or Epstein-Barr virus infections. Both types can also be seen in patients with lymphomas. (2)

Management

If the patient has symptomatic anemia, a blood transfusion should be given. High-dose corticosteroids of 1 to 1.5 mg/

kg may be started orally or intravenously depending on the patient's clinical status. Corticosteroids are continued at higher doses until the hematocrit level stabilizes. Then, corticosteroid therapy is weaned as the hemoglobin concentration continues to remain stable or increase. Corticosteroids are not discontinued until the DAT result becomes negative. Patients may require up to 6 months of therapy until stable remission is achieved. Splenectomy may be effective in patients with extravascular hemolysis or warm antibody-type hemolytic anemia. Rituximab is sometimes used for cold agglutinin syndrome AHA. Addressing the underlying disease process, such as infections or lymphomas, will help treat the cold agglutinin AHA as well. It is also important to maintain a normal body temperature because the hemolysis occurs if body temperatures drop below 98.6° F (37°C). (2)

Follow-up

Our patient was diagnosed as having complement-positive AHA or cold agglutinin syndrome with no identified infectious agent or malignant association. His Epstein-Barr virus and *Mycoplasma* serologic tests did not reveal an acute infection. He received high-dose corticosteroids immediately once his DAT result returned positive. He also received a blood transfusion when his hemoglobin level dropped below 5 mg/dL (50 g/L). Intravenous corticosteroids were continued until the hemoglobin level stabilized and he was no longer having hemoglobinuria. He was then followed by a hematologist with weekly laboratory tests, and once his DAT result became negative he was weaned off of corticosteroids over a 2-month period. He was also diagnosed as having iron deficiency anemia because further history revealed excessive cow's milk intake, and his laboratory tests showed a mean corpuscular volume at the lower limit of normal and a red blood cell distribution width at the upper limit of normal. After he was given an iron infusion, his reticulocyte count significantly increased and eventually normalized during corticosteroid therapy.

It was concluded that his initial reticulocyte count, although slightly elevated, was abnormally low for an anemic patient due to confounding iron deficiency anemia.

Lessons for the Clinician

- Hemolytic anemia is associated with an elevated reticulocyte count, elevated bilirubin level, elevated lactate dehydrogenase level, and decreased haptoglobin level.
- Consider hemolytic anemia as a diagnosis for patients with red or black urine due to hemoglobinuria.
- Hemoglobinuria is seen in intravascular hemolysis, which is present in complement-mediated autoimmune hemolytic anemia, also referred to as cold agglutinin syndrome.
- Direct antiglobulin or Coombs testing can help determine whether and which type of autoimmune hemolytic anemia is present.

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2 Fever, Chills, and Abdominal Pain in a 4-year-old Girl

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AUTHOR DISCLOSURE Drs Barrón Alemañy and Akarah have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy 4-year-old girl presents to a pediatrician's office for evaluation of fever and chills. The mother reports that the patient has not been feeling well for the past couple of days, with nausea, vomiting, decreased appetite, generalized abdominal pain, and decreased urine output. Medical and family histories are noncontributory. The mother and patient recently traveled to India for their yearly 1-month visit to family members and returned approximately 2 to 3 weeks ago. The primary care physician evaluated the patient with a rapid streptococcal test and a throat culture for streptococcal pharyngitis, a rapid antibody test for infectious mononucleosis, and a blood smear for malaria; all of these results were negative. On day 5 of illness, the patient is brought again to the primary care physician's office and is subsequently sent to the emergency department for further management. The patient has continued with persistent fevers and chills for the past 5 days. Her maximum measured temperature was 103°F (39.4°C) at home, and the mother reports that fevers subside with antipyretic use. On physical examination the patient is noted to have unremarkable vital signs, looks well, and has no significant findings. Therefore, the patient is discharged with instructions for supportive care for a likely viral illness given that her mother has tested positive for Epstein-Barr virus. Further blood test results eventually yield the diagnosis.

DISCUSSION

Multiple things have to be taken into consideration when a patient presents with these symptoms. Her travel history is important to the timing of presentation. Known diseases that are endemic to South Asia include malaria, dengue, chikungunya, enteric fevers, and leptospirosis, among others. All of these infections can present with fevers, and one thing that can help differentiate them could be the timing of incubation. When thinking of incubation in less than 10 days, we think more of infections such as dengue fever and chikungunya. These can also be accompanied by headaches, rash, myalgia, arthritis, and hemorrhages. Malaria and leptospirosis have an incubation period of days to months. The description of the fevers and constitutional symptoms can also be

helpful. With malaria we can see waxing and waning of fevers, accompanied by myalgia, anemia, nausea, vomiting, diarrhea, and abdominal pain. When there is a known exposure to animal urine or contaminated water, leptospirosis is high on the differential diagnosis.

Our patient presented with these symptoms at least 3 weeks after returning from travel, which helped us rule out some of these infections. Her peripheral blood smear was negative for malaria, and the preliminary report for the blood culture revealed growth of gram-negative rods.

Diagnosis

The blood culture's final identification revealed the organism to be *Salmonella typhi*.

Typhoid fever is not usually seen in the United States given that it is not an endemic area. This case pointed out that we should always take into consideration different types of etiologies for persistent fevers, reminding us of how important travel history is in all patients and their families.

Reviewing more about *S typhi*, this species has humans as the only host and reservoir, unlike other common types such as *Salmonella paratyphi*, which can infect animals. The transmission is mainly by consumption of contaminated food or water and occasionally by direct fecal-oral route. After ingestion and reaching the small intestine, the bacteria penetrate the intestinal mucosa and are ingested by macrophages, where they live and multiply. Afterward they reach the mesenteric lymph nodes and reach the bloodstream via the thoracic duct, causing primary bacteremia. The bacterium continues seeding and multiplying in the spleen, liver, gall bladder, bone marrow, and lymph nodes. It is here where they reside during the incubation period, which varies from 3 to 60 days. After multiplication in large numbers, bacteria spill into the bloodstream, creating the secondary bacteremia, and this prompts the initiation of clinical symptoms.

The patient's clinical manifestations include persistent fevers, abdominal pain, nausea, vomiting, diarrhea in children, constipation in adults, headache, malaise, and anorexia. Some cases may present with an exanthema characterized by "rose spots" on the chest, abdomen, and back. In more complicated cases, extraintestinal manifestations may occur, including melena, intestinal abscesses, intestinal perforation, altered mental status, meningitis, coma, and death.

Some patients become chronic carriers of the bacterium, estimated to be approximately 2% to 5% of those who had infection. This is defined as excretion of the organism in stool or urine for more than 12 months after an acute

infection. The bacteria persist in the biliary tract after symptoms resolve.

Typhoid fever is usually treated with a single antibiotic drug, but it depends on how severe the presentation of illness is, whether there are any local resistance patterns, the feasibility of taking oral medications, the clinical setting, and available resources. The usual choices are fluoroquinolones, with a duration of 7 to 10 days; third-generation cephalosporins, lasting 10 to 14 days; and azithromycin, prescribed for 5 to 7 days. Also used agents are chloramphenicol (duration, 2–3 weeks), ampicillin, or trimethoprim-sulfamethoxazole (duration of both, 10–14 days); but these are less frequently used given the prevalence of resistance. For patients with prolonged fever who require parenteral therapy, ceftriaxone is recommended as empirical therapy. Usually, defervescence is seen by day 4 or 5 of parenteral treatment. Once symptoms improve and susceptibilities have been tested, switching to oral antibiotics is appropriate.

The main mechanism of prevention would be avoiding ingestion of water and food in areas of poor sanitation and personal hygiene. There is also an indication for typhoid vaccination in travelers and individuals with a high risk of exposure. At the moment, there are 2 available vaccines: oral live vaccine and Vi capsular polysaccharide vaccine. Neither is completely effective against *S typhi*; therefore, routine vaccination is not recommended in the United States according to the Centers for Disease Control and Prevention (CDC) guidelines. Vaccination is recommended for those who are planning to travel to endemic regions, individuals who are in close contact with known carriers, and for those whose work exposes them to *S typhi*, such as microbiologists and laboratory workers.

Patient Course

Our patient was admitted for intravenous antibiotic therapy and was started on ceftriaxone, 1 g twice a day. Her fevers and symptoms continued for the first 4 days of hospitalization. By the fifth day she started having improvement of symptoms without nausea, vomiting, or diarrhea. Her fevers also started to subside by day 5. The blood culture sensitivities were also back and demonstrated susceptibility to trimethoprim-sulfamethoxazole. After being afebrile for 24 hours, the patient was transitioned to oral antibiotics for a total of 14 days of treatment. Of note, the patient's mother also tested positive for *S typhi* on blood culture and was started on oral antibiotics.

After discharge, the patient followed up with her pediatrician and continued to be afebrile and denied any recurrent symptoms of diarrhea or vomiting. She continued to

have positive stool cultures for *Salmonella* and is now considered to be a convalescent carrier.

Lessons for the Clinician

- Consider typhoid fever in patients with persistent fevers and a known travel history to resource-limited countries where these infections are endemic.
- Treatment should be started as quickly as possible to avoid severe complications such as intestinal abscesses, perforation, meningitis, coma, or death secondary to *Salmonella typhi* (typhoid fever).

- Knowing who is at higher risk to become infected with *S typhi* is important when discussing vaccination for the patient and/or family members.

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Case 2: Fever, Chills, and Abdominal Pain in a 4-year-old Girl

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2 New-Onset Seizure in a 5-year-old Boy with Autism Spectrum Disorder

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PRESENTATION

A 5-year-old white boy with autism spectrum disorder (ASD) presents to the emergency department toward the end of summer after a generalized tonic-clonic seizure event witnessed by his parents at home. Physical examination reveals bilateral wrist widening and genu valgus without rachitic rosary, frontal bossing, or Harrison groove. Initial testing demonstrates very low levels of total serum calcium of 4.4 mg/dL (1.1 mmol/L) (reference range, 9.2–11.0 mg/dL [2.3–2.8 mmol/L]) and ionized calcium of 2.9 mg/dL (0.7 mmol/L) (reference range, 4.5–5.6 mg/dL [1.1–1.4 mmol/L]); the serum phosphorus level is slightly elevated at 5.6 mg/dL (1.8 mmol/L) (reference range, 2.5–4.5 mg/dL [0.8–1.5 mmol/L]), with alkaline phosphatase slightly elevated at 381 U/L (6.4 μ kat/L) (reference range, 133–309 U/L [2.2–5.2 μ kat/L]). Further testing reveals an unmeasurable level of 25-hydroxyvitamin D (25-OHD) at less than 5 ng/mL (<12.5 nmol/L) and an elevated intact parathyroid hormone level of 108 pg/mL (108 ng/L) (reference range, 15–65 pg/mL [15–65 ng/L]).

Left knee radiography (Fig) demonstrates widening of the growth plate with metaphyseal widening and fraying predominantly in the distal femur, abnormal lucency in the metaphysis of the bones, and diffuse osteopenia. An initial electrocardiogram shows corrected QT interval prolongation consistent with hypocalcemia.

Regarding his history, he had been formally diagnosed as having ASD at age 3 years. Diagnosis of his ASD was met with early interventions, including speech, physical, and occupational therapies. On further questioning his parents note that he had a history of food selectivity even before his formal ASD diagnosis but has not received specific feeding interventions. Despite his very limited diet, he does not receive any vitamin supplements. He is not taking medications that could interfere with vitamin D and/or calcium metabolism. He tends to remain indoors, with very limited sunlight exposure. Interestingly, despite his very limited diet, his growth chart shows his body mass index plotting above the 85th percentile for age and sex.

DISCUSSION

Patient Course

Nutritional assessment of his diet based on 24-hour recall—consisting of almost the same daily quantities of cookies, French fries, and water—indicated that he was receiving only 360 mg of calcium daily (the recommended dietary allowance

AUTHOR DISCLOSURE Drs Shah and Marshall have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure. Left knee radiograph demonstrating growth plate widening, metaphyseal widening and fraying in the distal femur, abnormal lucency in metaphysis of bones, and diffuse osteopenia.

is 1,000 mg) and no vitamin D. He was diagnosed as having hypocalcemia with nutritional rickets due to severe calcium and vitamin D deficiency. Initial treatment with intravenous calcium normalized his serum calcium levels, with resolution of the electrocardiographic changes. Treatment was then switched to an oral calcium suspension providing 1,600 mg of elemental calcium daily. Oral vitamin D₃ therapy at 50,000 IU once weekly was started. Follow-up testing 2 days and 4 weeks after discharge showed normal total calcium levels at 9.4 mg/dL (2.4 mmol/L) and 10.1 mg/dL (2.4 mmol/L), respectively (reference range, 9.2–11.0 mg/dL [2.3–2.8 mmol/L]). He had also been referred to a feeding specialist while starting to receive a feeding intervention at school with a slight improvement in his diet.

The Condition

ASD is a complex developmental disorder characterized by varying degrees of impairment in 3 domains of functioning: communication, social behavior, and repetitive or stereotyped behaviors. (1) Recent reports of the incidence suggest that ASD occurs in approximately 1 in 68 children and is approximately 4.5 times more common in boys than in girls. (2) Children with ASD are more likely to demonstrate food selectivity (3) or picky eating, which is characterized by a restrictive repertoire of foods (4) due to avoidance of entire food groups, foods with a certain texture or a certain type, or solid foods.

Food selectivity and feeding problems are well described in children with ASD. (3)(5)(6)(7) A recent meta-analysis demonstrated that children with ASD were 5 times more likely to experience these issues than were children without ASD. (3) Unfortunately, these are often not detected by primary physicians during routine visits. This is partly due to lack of awareness to screen dietary habits in children with ASD. (3) In addition, exclusive use of the anthropometric parameters of height, weight, and body mass index often implies that these children with ASD are healthy due to consumption of sufficient calories to meet their energy requirements. (3)

Significantly lower serum 25-OHD levels have been demonstrated in children with ASD compared with control groups. (8)(9)(10)(11)(12) Possible explanations for differences in 25-OHD levels between these groups include lack of adequate sunlight exposure in children with ASD (13) due to less outdoor activity/more sedentary behavior, (14)(15) medications that interfere with vitamin D metabolism, (16) inflammation, (17)(18) and gastrointestinal issues. (19) Furthermore, a large proportion of children with ASD have lower vitamin D intakes than controls and do not meet their daily vitamin D requirements. (20)(21)(22)(23)

Another dietary factor that contributes to lower vitamin D and calcium levels is the adoption of the gluten-free, casein-free diet as an alternative therapy by many parents of children with ASD. (24) Gluten-free diets can eliminate cereals fortified with vitamin D, (25) and elimination of casein involves the avoidance of dairy products, which are also typically vitamin D fortified. (26) In addition, inadequate calcium intake contributes to lower calcium levels. (27)(28)(29)(30)

Although hypocalcemia as a result of nutritional rickets often presents as an asymptomatic laboratory finding, severe hypocalcemia can present as a life-threatening condition. Neuromuscular irritability, the hallmark of acute hypocalcemia, typically presents with numbness and tingling of the extremities and perioral region but in severe cases can result in bronchospasm and laryngospasm, (31) as well as seizures. (32) Cardiac electrophysiologic changes include prolongation of the QT interval due to lengthening of the ST segment. (33)

Although vitamin D deficiency is a main cause of nutritional rickets worldwide, in developing countries where calcium intake can be low, calcium deficiency itself is recognized as a major cause of nutritional rickets. (34) Historically, the main role of calcium deficiency in developed countries is to exacerbate the development of vitamin D-deficient rickets. (35) However, a single study in the United States by DeLucia et al (36) suggested that low

dietary calcium intake alone was responsible for nutritional rickets in toddlers whose dairy intakes are limited.

Implications

Consequences of reduced vitamin D levels in children with ASD include a negative effect on bone mineralization. Neumeyer et al (21) reported lower bone mineral density in peripubertal boys with ASD compared with controls. The lower bone mineral density was hypothesized to be due to both impaired vitamin D status and lower exercise activity. (20)

Vitamin D deficiency can also result in nutritional rickets. This is characterized clinically by osseous signs and symptoms that include swelling of the wrists, knees, and ankles; leg deformities (genu varum or valgus); rachitic rosary (enlarged costochondral joints); Harrison grooves (horizontal grooves consisting of the depressions of the sixth and seventh costal cartilages due to constant tension at the site of the attachment of the anterior portion of the diaphragm); frontal bossing; and bone pain, restlessness, and irritability. (37) Radiologic features include splaying, fraying, cupping, and coarse trabecular pattern of metaphyses, widening of the growth plate, and osteopenia. (38) Only 2 case reports have been published of patients presenting with nutritional rickets secondary to food selectivity in ASD. (38)(39) Clark et al (38) reported an 8-year-old boy with ASD who presented with hypocalcemia and clinical and

radiographic features of nutritional rickets due to vitamin D deficiency. This patient shared a very similar diet to our patient, consisting of French fries and water. (38) Stewart and Latif (39) reported a 15-year-old boy with ASD who also presented with nutritional rickets secondary to feeding difficulties. Supplementation of the diet with adequate vitamin D and other nutrients resulted in resolution of the rickets. (38)(39)

Lessons for the Clinician

- Careful screening by clinicians is essential for potential feeding issues, and accurate assessments should be considered of dietary intake of various essential nutrients to ensure that the recommended daily allowance for that specific age is met.
- Children with autism spectrum disorder may be at risk for poor nutrition because of their nontraditional eating habits.
- Dietary screening should complement anthropometric parameters of height, weight, and body mass index.
- Early intervention with nutritional and feeding therapies may be necessary in any child with autism spectrum disorder in whom feeding selectivity is appreciated.

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Case 2: New-Onset Seizure in a 5-year-old Boy with Autism Spectrum Disorder

Esha Shah and Ian Marshall
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3 Persistent Elevated Transaminase Levels in a 9-year-old Boy

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PRESENTATION

A 9-year-old overweight boy with seasonal allergies is referred to our gastroenterology service for persistently elevated transaminase levels for 6 months. His aspartate aminotransferase (AST) level is 90 U/L (1.5 μ kat/L) and alanine aminotransferase (ALT) level is 103 U/L (1.7 μ kat/L). In addition, he has an elevated cholesterol level (243 mg/dL [6.3 mmol/L]), a low high-density lipoprotein (HDL) cholesterol level (36 mg/dL [0.9 mmol/L]), and a borderline high triglyceride level (151 mg/dL [1.7 mmol/L]). On presentation he notes pain in the right upper quadrant that is dull, 5 of 10 in severity, and without aggravating or relieving factors. He recently had 3 loose, nonbloody, nonmucoid stools. He denies nausea, vomiting, chest pain, lower back pain, urinary frequency, or dysuria. His diet is rich in processed foods. His physical activity is minimal. He has no home medications or family history of liver disease. However, his 38-year-old father has an elevated cholesterol level and hypertension.

His BMI is between the 90th and 95th percentiles for age. His physical examination is significant for right and left upper quadrant tenderness on deep palpation without guarding or rigidity. He has no hepatosplenomegaly. Diet and exercise counseling is provided. The repeated transaminase levels are still elevated. Iron studies and ceruloplasmin levels are normal, and hepatitis panel, anti-smooth muscle/mitochondrial antibodies, liver-kidney microsomal antibody, α 1-antitrypsin phenotype, and antinuclear antibodies are all negative. Abdominal ultrasonography shows mild splenomegaly.

During his follow-up visit, the patient notes epigastric pain and intermittent loose stools. His celiac panel is negative, and his transaminase and lipid levels are persistently elevated (AST, 69 U/L [1.2 μ kat/L]; ALT, 100 U/L [1.7 μ kat/L]; cholesterol, 236 mg/dL [6.1 mmol/L]; HDL cholesterol, 32 mg/dL [0.8 mmol/L]; and triglycerides, 226 mg/dL [2.6 mmol/L]). Complete blood cell count and results of coagulation studies are normal. Despite diet and exercise, he has gained 5 kg. Compliance with lifestyle modifications is emphasized. Due to lack of specific etiology, the decision is made to perform a liver biopsy, which reveals the diagnosis.

DISCUSSION

Patient Course

The liver biopsy showed multiple macrophages filled with delicate material that stained positive for CD68, consistent with Niemann-Pick disease (NPD). Four

AUTHOR DISCLOSURE Drs Hsu and Josyabhatla have disclosed no financial relationships relevant to this article. Dr Monteiro has disclosed that she is a site investigator for Allergan Inc for an investigational drug for constipation. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

months later his abdominal pain improved but his transaminase, cholesterol, and triglyceride levels remained elevated. Genetic testing showed he was heterozygous for both the p.Q10X mutation and the p.W353L variant in the sphingomyelin phosphodiesterase 1 gene and had reduced sphingomyelinase activity, confirming the diagnosis. His parents and siblings are all carriers.

During a follow-up visit, he started to complain of shortness of breath. Chest radiography showed ground-glass opacities in both lung bases, consistent with interstitial disease. A computed tomographic scan of the chest was performed, which showed a diffuse miliary nodular pattern of interstitial disease with bibasilar predominance, consistent with NPD type B. The patient was seen by ophthalmology and neurology, and ocular and neurologic abnormalities were not identified, respectively. He is currently being managed with lifestyle modifications and close follow-up.

Differential Diagnosis and Evaluation

The differential diagnosis for children with elevated transaminase levels is very broad. This case raised a few important questions regarding the upper limit of normal for transaminase levels, screening for nonalcoholic fatty liver disease (NAFLD), and the approach for children with chronically elevated transaminase levels.

Elevated transaminase levels in an asymptomatic child are a common occurrence in the pediatric population, and researchers have proposed that current thresholds for transaminases should be lowered to improve sensitivity. Whereas AST is present in the cardiac muscle, skeletal muscle, kidney, brain, pancreas, lung, leukocytes, and erythrocytes, ALT is a more specific marker of liver damage. Researchers questioned the upper limit of normal for ALT levels because the median upper limit of normal of ALT levels at children's hospitals was 53 U/L (0.89 μ kat/L). (1) The Screening ALT for Elevation in Today's Youth study examined healthy adolescents and highlighted that the threshold for ALT levels was too high to detect chronic liver diseases such as hepatitis B, hepatitis C, and NAFLD because the threshold had a low sensitivity of 30% to 40%. Despite being freestanding children's hospitals, most children's hospitals in the United States are not using sex-specific thresholds for ALT levels, leading to wide variability among hospitals. When the National Health and Nutrition Examination Survey used sex-specific ALT thresholds of 25.8 U/L (0.43 μ kat/L) for boys and 22.1 U/L (0.37 μ kat/L) for girls, the sensitivity for detecting chronic liver disease doubled with only a minor reduction in specificity.

In this case, there was a high index of suspicion for NAFLD because the patient had risk factors such as being overweight, being male, and having dyslipidemia with a low HDL cholesterol level. Current North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guidelines state that there is no optimal age to start screening for NAFLD because there is a lack of pediatric studies on the incidence and disease progression. (2) However, NASPGHAN recognizes that screening high-risk patients is important because lifestyle changes, such as a healthy diet and exercise, can reverse NAFLD before it leads to advanced fibrosis. ALT can be used for screening because other methods, such as ultrasonography, magnetic resonance imaging, and computed tomography, are unreliable, are costly, and have increased radiation exposure, respectively. However, children with NAFLD can still have steatosis on ultrasonography even if they have a normal ALT level. Liver biopsy remains the gold standard for diagnosis, although there is no consensus on the optimal timing for biopsy.

The approach to a child with elevated transaminase levels is debatable. A fluctuating pattern for elevated transaminase levels is common; therefore, retesting is recommended. In a retrospective study, researchers concluded that the elevated transaminase levels in healthy children were mostly benign, and liver biopsy provides minimal contribution. (3) Others have favored a more aggressive approach to evaluating abnormal transaminase levels because chronically elevated transaminase levels can suggest an underlying liver disorder. (4) In diseases such as hepatitis B, autoimmune hepatitis, NAFLD, and Wilson disease, early detection can lead to favorable outcomes and prevent progression to fibrosis and cirrhosis. (5)(6)(7)(8) Two retrospective studies found that 9% to 12% of isolated elevations in transaminase levels were due to genetic disease. (5)(9) Patients with inborn errors of metabolism and congenital disorders involving the liver can be asymptomatic and may be underdiagnosed if evaluation is inadequate. (10)

Currently, there is no standard diagnostic algorithm but there are several approaches to elevated transaminase levels based on literature review and expert opinion. (4)(6)(10) An initial evaluation should include a thorough history and physical examination. The history should include an investigation of symptoms, drug ingestion, risk factors for viral hepatitis, autoimmune or metabolic disorders, and consanguinity. Duchenne and Becker muscular dystrophies can also present as isolated elevated transaminase levels and should be ruled out. (11)

The timing of retesting remains a question. Before repeated laboratory testing, the patient should temporarily discontinue hepatotoxic medications and limit exercise, which can lead to elevated transaminase levels. AST and ALT measurements should be repeated, along with γ -glutamyl transferase and creatine phosphokinase, because patients can have spontaneous normalization of transaminase levels ranging from 26% to 73.6%. (5)(9) γ -Glutamyl transferase rather than alkaline phosphatase values are more useful to differentiate hepatocellular from cholestatic causes (10). Viral markers of infection, hypothyroidism, endocrine disorders, autoimmune hepatitis, Wilson disease, hemolytic disorders, and metabolic disorders are also part of tier 1 or 2 of the evaluation. Further investigation includes ultrasonography of the liver and biliary tree to rule out acute obstruction.

Liver biopsy is generally reserved for cases when enzymes and other noninvasive diagnostic tests are inconclusive but can be an essential tool to distinguish among hepatitis, cholestasis, steatosis, infectious disease, and storage or infiltrative disease and aid in prognosis. (12) Evaluation using liver biopsy has been better studied in adults with elevated transaminase levels, but even in adults, the utility of liver biopsies in changing diagnosis and management has been variable. (13)(14) According to the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, the indications for liver biopsy are evolving as other less invasive measures can replace biopsy in some situations. (15) However, liver biopsy remains the standard for obtaining histopathologic markers for metabolic conditions and can be used to assess the severity and progression of liver disease.

In this case, our patient had an extensive evaluation before his diagnosis and raises the question regarding the cost-effectiveness of his evaluation. Although mild splenomegaly was picked up on initial ultrasonography, the cause was attributed to a primary liver pathology given the persistently elevated transaminase levels. Mild splenomegaly in the pediatric population is most often due to a viral infection (Epstein-Barr virus, cytomegalovirus, or human immunodeficiency virus). Other important causes of splenomegaly broadly include hematologic disorders, infiltrative disorders, congestive splenomegaly, and chronic inflammatory diseases. However, given the paucity of his symptoms, normal blood cell counts, and lack of splenomegaly on initial and subsequent physical examinations, the focus remained on his elevated transaminase levels. The authors speculate whether the chest radiograph could have served as a simple screening test. The finding of interstitial lung disease might have then changed the approach in the

context of mild splenomegaly and elevated transaminase levels in an overweight child, and acid sphingomyelinase assay may have then preceded a more invasive test such as a liver biopsy. However, a chest radiograph was not obtained initially because he did not have respiratory symptoms at presentation.

Actual Diagnosis

NPD is a rare genetic disorder that encompasses a family of diseases, including primary acid sphingomyelinase deficiency (types A and B) and an endosomal-lysosomal trafficking disorder (type C). (16)(17) Types A and B are caused by mutations in the sphingomyelin phosphodiesterase 1 gene (*SMPD1*), which results in deficient activity of acid sphingomyelinase and subsequent accumulation of sphingomyelin in the central nervous system and nonneural tissue. (18) Patients with type A NPD are healthy at birth but develop hepatosplenomegaly, lymphadenopathy, and motor delays by 6 months of age, followed by regression and death by age 3 years. Type B NPD typically presents with hepatosplenomegaly, thrombocytopenia, delayed skeletal maturation, interstitial lung disease, hyperlipidemia, and ocular changes without neurologic involvement. (18)(19)(20)(21) Type C NPD is caused by mutations in *NPC1* and *NPC2* genes, resulting in lipid accumulation in lysosomes. (17) Type C can have a range of presentations from a fatal progressive disease starting from infancy to a neurodegenerative disease in adulthood. The diagnostic approach to NPD depends on the suspected subtype.

Type A and B NPD are diagnosed by acid sphingomyelinase deficiency and mutations in the *SMPD1* gene. Diagnosis of type C NPD has undergone recent changes. Filipin stain positivity in cultured fibroblasts or mutations in *NPC1* or *NPC2* genes used to be first line. They have been replaced by an assay of plasma oxysterols, a simple and rapid screening test. If the biomarkers are suspicious for NPD, the diagnosis can be confirmed with *NPC1* and *NPC2* sequencing.

Treatment/Management

Currently, there is no recommended definitive treatment for NPD, and supportive measures are encouraged. (16) Type A NPD should have physical and occupational therapy and nutrition monitoring to assess their growth. Type B NPD should have routine follow-up every 6 to 12 months to assess growth, nutrition, bleeding, shortness of breath, and abdominal pain. Although there is no approved treatment for type B NPD, research is currently being conducted with enzyme therapy and gene splicing therapy. (22) (23) Miglustat, an inhibitor of glycosphingolipid synthesis,

has been approved for the treatment of type C NPD in Europe.

Lessons for the Clinician

- Niemann-Pick disease is a genetic disorder that should be considered in a child with abdominal pain and persistently elevated transaminase levels.
- The evaluation of children with elevated transaminase levels lacks standardization. The definition of elevated transaminase levels should better reflect the age- and sex-based norms for healthy children.
- Future studies should be directed toward the development and evaluation of a systematic approach to

elevated transaminase levels because early detection may improve prognosis.

- The necessity of performing a liver biopsy remains controversial and a consensus regarding the timing and utility of liver biopsy has yet to be reached.

Note: This case is based on a poster presentation by Drs I.M. Monteiro and W. Attia at the Annual Meeting of the North American Society for Pediatric Gastroenterology and Nutrition, Washington, DC, October 8, 2015. Poster No. 488.

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Case 3: Persistent Elevated Transaminase Levels in a 9-year-old Boy

Diane Hsu, Rohit Josyabhatla and Iona M. Monteiro

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3 An 11-month-old Boy with New Bradycardia

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AUTHOR DISCLOSURE Drs Folker and May have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An 11-month-old boy is brought to the emergency department for 1 day of decreased appetite, vomiting, and diarrhea. His parents have both been ill with similar symptoms, and the boy tests positive for **norovirus**. In the course of his evaluation, he is found to be significantly bradycardic, with a heart rate varying from **55 to 65** beats/min. His parents report an uneventful prenatal and birth history, and he has since been a healthy child. Notably, recorded heart rates were age appropriate at all previous health maintenance visits.

On examination he is fussy but consolable and is in no distress. He is afebrile, with a normal blood pressure and respiratory rate for age. He is attentive and interactive. His head is atraumatic and normocephalic, with a soft and flat anterior fontanelle. His pupils are equal, round, and reactive to light. His mucous membranes are moist, and he makes tears when he cries. Radial, brachial, and femoral pulses are of normal strength. Cardiac auscultation confirms a **heart rate of 65 beat/min, a regular rhythm, and normal S₁ and S₂ sounds with physiologic splitting**. There are no murmurs or extra heart sounds. His distal extremities are well-perfused and have a capillary refill time of less than 2 seconds. His lung fields are clear. His bowel sounds are hyperactive, and his abdomen is without hepatosplenomegaly. He has no rashes. His neurologic examination findings are grossly normal. An electrocardiogram (ECG) is ordered to further assess his bradycardia (Fig 1).

DISCUSSION

Differential and Actual Diagnoses

This ECG may appear at first glance to show sinus bradycardia; however, closer examination of the patient's ECG reveals a **variable PR interval and unusual and varying T-wave morphology**, best noted in the lead II rhythm strip. The notching of the T waves occurs because of P waves (atrial depolarization) falling on T waves (ventricular repolarization). Our differential diagnosis focused on the following 3 categories as the etiology of this notching: **atrial depolarization occurring too early, ventricular repolarization occurring too late, and atrioventricular (AV) block**.

Early atrial depolarization could be caused by either an early sinus beat or an ectopic atrial focus. In the case of a premature atrial contraction (PAC), we would typically see a P wave arriving earlier than expected, along with variation in P-wave morphology, neither of which was apparent in this patient. Moreover, PACs that

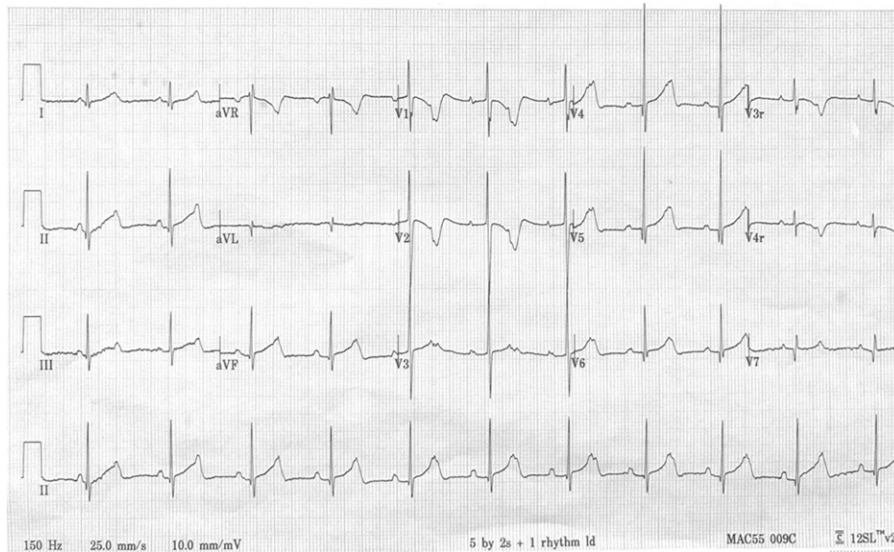


Figure 1. Electrocardiogram obtained at the time of presentation to the emergency department shows a narrow complex rhythm at a bradycardic rate for age (65 beats/min). Close examination reveals an inconsistent PR interval, along with variable notching of the T waves caused by buried P waves. The axis is normal for age, and the **QTC is not prolonged (0.42 seconds)**. This image is consistent with **third-degree atrioventricular block with a junctional escape rhythm**.

occur during ventricular repolarization may fall in the absolute refractory period and fail to conduct (blocked PAC) or in the relative refractory period and conduct, albeit with slowed ventricular depolarization represented as a widened QRS complex (PAC with aberrancy). In this patient's ECG, even P waves occurring late in the T wave fail to conduct, making PACs an unlikely cause of the patient's abnormal ECG findings.

Prolonged ventricular repolarization would be seen on ECG as a **long QT interval**. In this case, normally timed atrial depolarization may occur before the completion of repolarization from the previous ventricular beat. This can be seen in patients with long QT syndrome or rarely from electrolyte disturbances or medication effect. In this patient, the corrected QT interval measured 0.42 seconds, falling in the normal range and eliminating late ventricular repolarization from the differential diagnosis.

P waves can also fall on T waves in various degrees of AV block. In Mobitz types I and II second-degree AV block, the nonconducted P wave can overlap the T-wave complex; however, typical Mobitz I and II patterns are not seen on this patient's ECGs. In 2:1 AV block, every second P wave is nonconducted and can fall on the T wave, and the conducted P wave does so at a normal and consistent PR interval. Second-degree 2:1 block seems unlikely for this patient's ECG, given the slight variability in the PR interval that is noted; however, this could be confirmed by examining more extended rhythm monitoring.

In third-degree AV block, P waves can fall on T waves arbitrarily, due to complete dissociation between atrial and

ventricular depolarization. This diagnosis can be confirmed by assessing relatively **consistent P-P and R-R intervals independently**. This patient's P waves march out at consistent 0.46-second intervals, which would correspond with an appropriate heart rate of 130 beats/min (Fig 2A). The QRS complexes march out at 0.92-second intervals (corresponding with the recorded heart rate of 65 beats/min) and are narrow complex with a normal axis for age. This finding makes third-degree AV block with a junctional escape rhythm the most likely explanation for this child's bradycardia.

The Condition

Third-degree AV block most commonly occurs in infants and young children with complete congenital AV block (CCAVB), often the result of **maternal antibodies** cross-reacting with fetal conduction tissue in neonatal lupus. **Anti-Ro (SSA) and anti-La (SSB)** are the most common associated serologic markers. This patient had no clinical features of neonatal lupus, and both he and his mother tested negative for these antibodies. Along with his previously normal heart rates for age, this makes CCAVB unlikely.

Acquired AV block has a broad differential diagnosis, including infectious, genetic, and idiopathic etiologies. The patient had no family history of rhythm abnormalities, pacemaker placement, or myopathies. Echocardiogram showed normal anatomy with mild left ventricle enlargement. Of note, there was no left atrial isomerism or

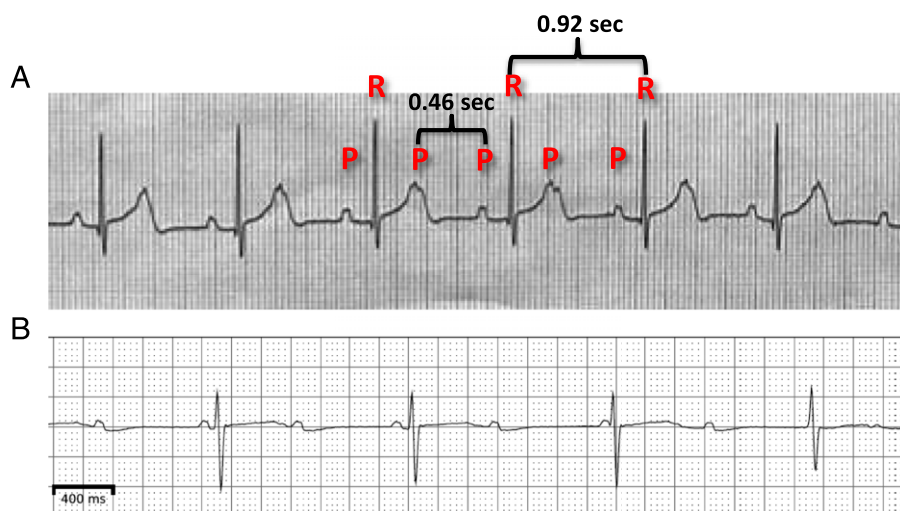


Figure 2. A. Electrocardiogram tracing taken from the lead II rhythm strip in Fig 1. "P" and "R" designate P and R waves, respectively. The patient's P waves march out at 0.46-second intervals, and the narrow QRS complexes march out at 0.92-second intervals. B. A separate electrocardiogram tracing taken from the same patient during his hospital stay more clearly demonstrates the complete dissociation between the P and R wave complexes that is typical for third-degree atrioventricular block. The patient's junctional escape rate is 40 to 45 beats/min at the time of this tracing.

L-transposition of the great arteries. Biventricular function was normal, with left ventricular ejection fraction of 70%, likely demonstrating a physiologic compensatory increase in stroke volume to maintain cardiac output. This high ejection fraction supported the hypothesis that his AV block had been present for some time, likely well before his acute norovirus symptoms.

A comprehensive evaluation for evidence of infectious etiologies (including *Borrelia burgdorferi*, mycoplasma, cytomegalovirus, rubella, influenza A and B, Coxsackie, echovirus, and adenovirus) as well as a chromosomal microarray and a 105-gene cardiomyopathy panel were negative. After an extensive evaluation, the diagnosis of acquired AV block was deemed to be idiopathic and coincidental to his norovirus infection.

Natural History and Treatment

The decision to place a permanent pacemaker can be complicated in young children, especially when the underlying cause of acquired AV block is unknown. Given the absence of randomized trials investigating pacemaker placement in young children, most recommendations are based on 2008 consensus guidelines that recommend pacemaker placement in pediatric patients with 1) advanced and symptomatic second- or third-degree AV block, 2) sinus node dysfunction causing symptomatic bradycardia, 3) persistent postoperative second- or third-degree AV block, or 4) CCAVB with wide QRS escape rhythm, complex ventricular ectopy, ventricular dysfunction, or a ventricular rate less than 55 beats/min. (1) None of these immediate indicators applied to our patient.

Given the patient's young age and small size, transvenous pacemaker placement would put him at increased risk for venous obstruction, (2) so epicardial (surgical) placement would be preferred. He would likely need additional surgical modifications to the device and leads as he grew. Considering this and the patient's current stability, the family and cardiology team made a shared decision to delay device placement with close cardiology follow-up.

Using the natural history of CCAVB as a proxy for this patient's anticipated course, we expect that he will require a pacemaker in the future. Patients with CCAVB typically experience decreasing ventricular rates over time and can begin to experience symptoms such as anxiety, poor school performance, sleep disturbances, and syncope at any age. (3) (4) Over time, echocardiography may show left ventricular dilation, abnormal wall stress, and AV valve dysfunction. Placement of a transvenous pacemaker later in childhood can often alleviate these findings, and the 2008 consensus guidelines support doing so electively for children and adolescents (class IIb recommendation). (1)

Patient Course

The patient was admitted to the hospital to monitor his trajectory. His electrolytes and inflammatory markers were normal, and he quickly recovered from his gastroenteritis symptoms. Ongoing telemetry more clearly confirmed the diagnosis of third-degree AV block (Fig 2B). His heart rate varied from 44 beats/min during sleep to 80 beats/min during peak activity. More than 52 hours of periodic ambulatory rhythm monitoring was analyzed on follow-up and demonstrated an average heart rate of 59 beats/min. The

slowest recorded heart rate was 44 beats/min without any superimposed pauses. There were no instances of wide complex escape rhythm, ventricular ectopy, or ventricular arrhythmia to prompt early pacemaker placement. One year later, he remains in a stable junctional escape rhythm and is being closely monitored for eventual pacemaker placement.

Summary

On presentation with unexplained bradycardia, this child had an electrocardiogram (ECG) performed that could easily be mistaken for sinus bradycardia at first glance. However, much like the saying "even a broken clock is right twice a day," the patient's atrial rate, which was nearly twice the junctional escape rate, aligned on this ECG in such a way that simply gave the illusion of sinus conduction. Closer examination reveals abnormal PR variability and T-wave notching from buried P waves. These clues led to the final diagnosis of acquired third-degree atrioventricular block, which was deemed to be idiopathic in nature.

Lessons for the Clinician

- Acquired third-degree atrioventricular (AV) block, although less common in young children than congenital AV block, should be included in the differential diagnosis for bradycardia in pediatric patients.
- Abnormal T-wave morphology on electrocardiogram should alert the clinician to consider repolarization abnormalities, along with premature atrial contractions, long QT syndrome, and AV block.
- The decision to place a permanent pacemaker in a young child is complicated, with major indicators including the presence of symptoms or an unstable escape rhythm (among others).

Note. The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or US Government.

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3 Persistent Fussiness in a 2-month-old Girl

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PRESENTATION

A 2-month-old girl is referred from her primary care provider for evaluation of persistent fussiness. Symptoms began 2 days earlier. She had been evaluated by an urgent care center at the time of symptom onset. There she was diagnosed as having colic and given instructions for supportive measures at home. Since onset, she continues to cry for long stretches and is consolable only after being picked up or held semiprone. Her cry is softer than normal. Mother denies any fevers, cough, congestion, eye discharge, abdominal distention, discolored stool, or rashes. Despite being more difficult to console, she has continued to feed from both breast and bottle without a decrease in wet or dirty diapers.

Vital signs are as follows: temperature, 98.6°F (37.0°C); heart rate, 169 beats/min; respiratory rate, 40 breaths/min; blood pressure, 82/60 mm Hg; and oxygen saturation, 98% on room air. From the bedside, she is vigorous with an audible cry. The anterior fontanelle is open and flat. Respirations are unlabored without adventitious sounds or accessory muscle use. The abdomen is nontender with active bowel sounds and without any palpable masses or hepatosplenomegaly. Careful examination of the digits demonstrates no evidence of hair tourniquet. The remainder of the examination findings are within normal limits.

Plain films of the chest and abdomen are within normal limits. Blood and urine culture samples are collected. Laboratory evaluation reveals the following: a white blood cell count of 19,800/ μ L (19.8×10^9 /L), with 72% neutrophils, 13% lymphocytes, 9% monocytes, and 0% monocytes; a hemoglobin level of 11.6 g/dL (116 g/L); and platelet count of 681 $\times 10^3$ / μ L (681×10^9 /L). Urinalysis of a catheterized urine sample reveals yellow color, cloudy appearance, specific gravity of 1.025, pH 6.0, negative leukocyte esterase and nitrite, and trace ketones. The C-reactive protein level is 8.2 mg/L (78.0 nmol/L).

She is admitted to a general pediatrics service for continued observation without initiation of antibiotic drug therapy. On the second day of admission she develops positional stridor, refusal of oral intake, and a low-grade fever of 100.8°F (38.2°C). Repeated laboratory studies are significant for a C-reactive protein level of 143 mg/L (1,361.9 nmol/L). An additional radiography study confirms the diagnosis (Fig) and prompts additional interventions.

DISCUSSION

The lateral neck radiograph demonstrated thickening of the retropharyngeal soft tissues with focal lucencies, likely representing air, compatible with a

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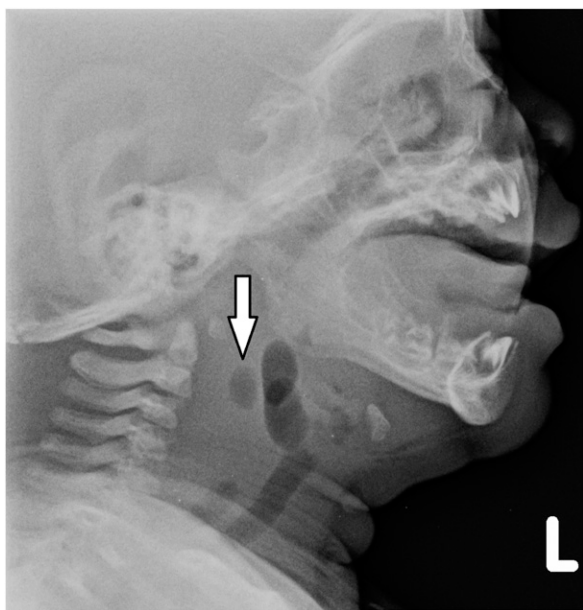


Figure. Lateral neck radiograph highlighting radiolucency in retropharyngeal space (arrow) concerning for free air.

retropharyngeal abscess. Cross-sectional imaging confirmed the suspected diagnosis, demonstrating ill-defined enlargement of the retropharyngeal soft tissue with fluid and gas causing anterior displacement of the trachea. In consultation with otolaryngology, she was transferred to the ICU for close monitoring, attempted surgical drainage, and an extended course of intravenous antibiotic agents, including vancomycin and ampicillin-sulbactam. She gradually recovered without any residual swallowing dysfunction. An esophagram demonstrated no evidence of diverticulum, and a follow-up outpatient direct laryngobronchoscopy demonstrated only mild soft tissue redundancy with mild tracheomalacia.

The Condition

Retropharyngeal abscesses form in the potential space between the posterior pharyngeal wall and prevertebral fascia occupied by the paramedial lymph node chains that filter lymph from the nasopharynx and paranasal sinuses. Simple infection or trauma can lead to lymph node enlargement, necrosis, and potential for phlegmonous change preceding frank abscess formation. Patients with a retropharyngeal abscess typically have a constellation of symptoms, including fever, neck pain or stiffness, and a change in voice quality. As symptoms progress, patients can develop difficulty handling secretions, odynophagia, and stridor with or without respiratory distress.

Untreated, retropharyngeal abscess can have severe clinical sequelae. The infection can serve as a nidus for

septicemia. Localized swelling and inflammation can lead to airway obstruction, and in severe cases, erosion through the soft tissue can lead to thrombophlebitis of the internal jugular vein (Lemierre disease). The neonatal population in particular seems to be more vulnerable to direct extension into the mediastinum and the resultant mediastinitis or cavitary pneumonia. (1)(2)

Diagnosis

The diagnosis of retropharyngeal abscess is rare in infants younger than 3 months without a history of airway trauma. Reported symptoms include respiratory distress, poor feeding, and irritability with or without fever at the time of presentation. The diagnosis can be confirmed on a lateral neck radiograph with full neck extension, where evidence of widening of the retropharyngeal space or mass effect would be seen. Cross-sectional imaging can be a valuable tool in confirming the diagnosis and guiding potential surgical interventions. (3)

Treatment

All patients should be thoroughly assessed for indications of airway compromise requiring immediate attention. Broad spectrum antibiotic agents, with potential surgical drainage, remain the mainstay of management. Infections are typically polymicrobial, including *Streptococcus pyogenes*, non-group A *Streptococcus*, *Staphylococcus aureus* (methicillin susceptible and resistant), and anaerobic species, including *Prevotella*, *Bacteroides*, and *Peptostreptococcus*. (4)(5) Clindamycin or ampicillin-sulbactam provide adequate coverage in most scenarios, although the addition of vancomycin in the ill-appearing patient or in the patient with positive blood cultures is appropriate. Nearly 80% of patients with abscesses smaller than 20 mm improve within 48 hours with antibiotic drug therapy and conservative management alone. Patients with abscesses larger than 25 mm or those who fail to improve on antibiotic drug therapy are more likely to require surgical intervention. In all cases, the risk of iatrogenic injury from surgery needs to be weighed against the risk of antibiotic drug resistance and prolonged hospitalization. (6)

Differential Diagnosis

Persistent fussiness in infants with otherwise normal physical examination findings should raise the suspicion for serious underlying conditions. Focused history and examination looking for evidence of infection, accidental and nonaccidental trauma, corneal abrasions, hair tourniquets, or intestinal obstruction are always indicated.

Retropharyngeal abscesses, although rare in neonates, can have an indolent presentation and should be considered in the setting of persistent oral refusal, fussiness, and upper airway signs.

Lessons for the Clinician

- Acute onset of fever, odynophagia, neck stiffness, hoarse voice, and difficulty with secretions should raise the suspicion for a potential retropharyngeal abscess. Children younger than 6 months may have a more insidious onset at the time of presentation.
- Ensuring a stable airway should take priority in all patients; the diagnosis can be confirmed with lateral neck radiography or cross-sectional imaging.
- Conservative management with targeted antibiotic drug therapy may be appropriate for stable children with small abscesses; however, children with protracted courses or large collections should be evaluated by otolaryngology for possible surgical intervention.

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Case 3: Persistent Fussiness in a 2-month-old Girl
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3 Unexpected Diagnosis in a Febrile Infant

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PRESENTATION

A 34-day-old white boy presents to the emergency department with a fever (101.8° F [38.8°C]) and a 1-day history of poor feeding and fussiness. There is no other history of acute illness, although his older brother currently has oral ulcers secondary to a viral illness. He was born at term after an uncomplicated pregnancy. Maternal prenatal infection screening, including group B *Streptococcus*, was negative. He was discharged on the second day after birth and had been breastfeeding with good weight gain until the day before admission. Vascular access is obtained, a sepsis evaluation is initiated, and he is treated empirically with ampicillin, cefepime, and acyclovir.

He is admitted to the PICU due to concern for sepsis, where on examination he is awake, alert, and crying. The anterior fontanelle is soft and flat, the tympanic membranes are normal, and the oral mucosa appears pink and moist without lesions. Neurologic examination demonstrates normal tone and strength, and there are no focal deficits. The remainder of the physical examination findings are normal.

Laboratory studies are significant for a white blood cell count of 2,800/ μ L (2.8×10^9 /L), with an absolute neutrophil count of 180/ μ L (0.18×10^9 /L). Results of cerebrospinal fluid (CSF) studies show a total protein level of 0.118 g/dL (1.18 g/L), glucose level of 56 mg/dL (3.1 mmol/L), white blood cell count of 13/ μ L (0.013×10^9 /L), and red blood cell count of 0.052×10^6 / μ L (0.052×10^{12} /L). The Gram-stain showed no organisms. Herpes simplex and enterovirus polymerase chain reaction (PCR) results are negative. The remainder of the laboratory findings, including basic metabolic panel, respiratory viral panel, C-reactive protein level, and chest radiograph, are normal.

DISCUSSION

While in the PICU the patient remained afebrile, and his fussiness and enteral intake returned to baseline. On the second hospital day we were notified that our laboratory had been testing a new PCR test awaiting Food and Drug Administration (FDA) approval, which they had run on our patient's CSF sample. They reported that his sample was positive for parechovirus. Although parechovirus is well described in the literature and well-known among pediatric infectious disease specialists, it is less familiar to general pediatricians and other pediatric subspecialists.

AUTHOR DISCLOSURE Drs Kolker, Halyko, and Tigges have disclosed no financial relationships relevant to this article. Dr Halyko's current affiliation is Aurora Healthcare, Waterford, WI. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Human parechoviruses (HPeVs) are single-stranded, positive sense RNA viruses that belong to the large family of Picornaviridae. They were first discovered during a diarrheal outbreak in the United States more than 50 years ago and were initially described as echovirus 22 and 23 based on their similar clinical presentation and cytopathology with enteroviruses. Recently, the viruses have been reclassified into their own genus, with 16 currently recognized types labeled HPeV1 to HPeV16. HPeV1 and HPeV2 are the formerly named echoviruses 22 and 23, which represent the most prevalent forms of parechovirus.

Parechoviruses have been known to be a cause of infection in children, and most of these infections occur within the first year after birth. Seropositivity for parechovirus antibody to HPeV1 increased from 22% at 2 months of age to 88% at 2 years, confirming the very high incidence of HPeV1 infection in early childhood. (1) Similar results have been seen with HPeV3.

HPeV1 is the most prevalent parechovirus and generally causes gastrointestinal or respiratory illness. HPeV1 has also been found in sporadic cases of aseptic meningitis, with these infections being more prevalent in the late summer and early winter months. (2)(3)

Recently, HPeV3 has emerged as a common cause of meningitis and neonatal sepsis. The presentation of HPeV3 infection is similar to that of enterovirus, with fever, seizure, irritability, rash, and feeding problems. In a Scottish study, HPeV was reported in 14 of 1,575 CSF samples. All of these patients were younger than 3 months, and further studies determined that HPeV3 was the source for all these infections. (1) This study, as well as others, suggests that HPeV3 has a propensity for causing central nervous system (CNS) infection. Other investigators have used real-time PCR to study the replication of HPeV1 and HPeV3 in gastrointestinal, respiratory, and neuronal cell lines. They found no significant difference in the rate of replication of HPeV1 in various cells but found that HPeV3 strains replicated more rapidly in neuronal cells. (1)(4)

Although HPeV3 has been associated with relatively benign cases of meningitis and neonatal sepsis, it also has been shown to cause more severe CNS infection, including encephalitis. The Australian Childhood Encephalitis Study identified 13 cases of suspected HPeV encephalitis. They did not type these HPeV infections, although they hypothesized that HPeV3 was the cause because of its relative prevalence. In this study, 9 of the 13 patients had confirmed encephalitis as deemed by an expert panel, and the other 4 patients were classified as not having

encephalitis but had positive CSF PCR for HPeV. The study found that there were significant neurodevelopmental concerns at 12 months in 7 of 8 children in the encephalitis cohort. There were no neurodevelopmental concerns in the 4 patients in the nonencephalitis cohort. (5)

To date, HPeV meningitis has been hypothesized to have similar neurodevelopmental outcomes to that of enterovirus meningitis. Many long-term studies have been performed to assess the outcomes of enteroviral meningitis and have demonstrated no significant long-term neurodevelopmental abnormalities for children with mild CNS involvement. For children with more severe CNS involvement, including encephalitis and/or CNS involvement leading to cardiopulmonary failure, neurodevelopmental outcomes have not been as good. (2) Long-term studies have not yet been performed in populations with HPeV meningitis.

Although it may be intuitive, several studies have suggested older siblings as a primary source of infection. A Dutch study found that second-born children had a 9-fold increased risk of developing HPeV3 infection and an 11-fold increased risk if siblings were less than 2 years apart in age. (6) Finally, a Japanese study of 43 neonates and young infants with HPeV3 found that the infants infected with HPeV3 were more likely to have siblings than the general population. These findings suggest that older siblings are a likely source for HPeV infection in neonates, and the presence of an older sibling may increase the index of suspicion for parechovirus infection. (7)

The true incidence and prevalence of HPeV meningitis and encephalitis are likely underreported due to lack of routine testing. As mentioned previously herein, at the time of presentation our institution did not have an available approved test for HPeV. Lack of testing for HPeV has important clinical consequences. Access to PCR for HPeV could lead to decreased use of antibiotic agents and longer length of stay in patients found to be HPeV positive, similar to patients found to be enterovirus positive. These consequences support the need for a fast and reliable test for HPeV.

A newly approved PCR test that can detect 14 pathogens including HPeV holds promise for increasing the ability to diagnose HPeV meningitis and encephalitis. In a multicenter evaluation, the sensitivity and specificity for HPeV were 100% and 99.8%, respectively. (8) HPeV testing could potentially allow for the more prudent use of antibiotic drugs, decreased length of hospital stay, and better informed counseling of patients' families.

Although infection with HPeV is common, no antiviral medications are currently approved. (2) An oral viral

capsid inhibitor, pleconaril, has been shown to have activity against viruses from the Picornaviridae family. Abzug et al performed a randomized controlled trial and reported a shorter time to PCR and culture negativity, as well as greater survival, in neonates with enteroviral sepsis who received pleconaril. (9) Other additional studies have suggested benefit for pleconaril recipients and have demonstrated that pleconaril is generally well-tolerated, but clinical outcome in treated patients varied considerably. Administration of intravenous immunoglobulin is an additional treatment option, but the outcome was variable with this treatment as well. In summary, more studies are needed to evaluate the effectiveness of antiviral medications, and current treatment consists of supportive care.

Although he remained clinically stable, our patient was hospitalized on prophylactic ceftazidime until his absolute neutrophil count was greater than 500/ μ L (0.50×10^9 /L). He was subsequently discharged on hospital day 6 without sequelae.

Lessons for the Clinician

- Parechoviruses are a well-known but underrecognized source of infection and fever in infants.
- The use of new polymerase chain reaction testing allows for quick identification of parechoviral infections.
- Parechoviruses commonly cause gastrointestinal and/or respiratory illnesses but are also known to cause central nervous system (CNS) infections as well.
- Mild CNS infections are thought to be well tolerated, similar to enteroviral CNS infections, without significant neurodevelopmental deficits.
- More serious infections associated with encephalitis may result in neurodevelopmental deficits, but more research is needed to understand its true effects.
- Pediatric health-care providers should be aware of parechovirus as a potential cause of fever in neonates and be prepared to counsel families on its treatment, expected course, and long-term outcomes.

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3 Hepatosplenomegaly with Hyperpigmentation in a 6-year-old Girl

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PRESENTATION

A 6-year-old girl of eastern Himalayan origin presents with a 1-year history of recurring fever and abdominal pain. The fever is intermittent and high grade, associated with chills and sweating, with recurrences every 2 to 3 weeks. She also reports left flank and abdominal pain, with some associated distention. She feels full easily during meals and often wakes up from sleep due to pain. There is no pedal edema, breathlessness, decreased urination, or facial puffiness. She feels easily fatigued and is described as getting more “white” by the parents. Her family and developmental histories are normal. Details of previous evaluation and care are not available.

On examination, she appears pale, quiet, and lethargic. Her pulse is 118 beats/min, her blood pressure 94/60 mm Hg, her respiratory rate is 22 beats/min, and her temperature is 101.2°F (38.4°C). Her weight and height are less than the third percentile. Diffuse hyperpigmentation is noted. There is no cyanosis, lymphadenopathy, clubbing, edema, or icterus. Abdominal examination reveals an increased girth of 46.5 cm, prominent veins, a firm liver edge 4.5 cm below the right costal margin with a liver span of 11 cm, and a massive spleen span of 11.5 cm. Results of the cardiovascular, respiratory, and central nervous system examinations are normal.

She has normal liver enzyme levels and a normal coagulation profile. Her renal function test results and electrolyte levels are normal. Her serum total protein level is elevated at 9.70 g/dL (97 g/L) (reference range, 6–8 g/dL [60–80 g/L]), and her globulin levels are elevated at 7.00 g/dL (reference range, 2.0–3.5 g/dL). The sedimentation rate is elevated at 60 mm/hour. The hemoglobin level is low at 7.1 g/dL (71 g/L) with a mean corpuscular volume of 75.1 μm^3 (75.1 fL). The white blood cell count is normal at 8,000/ μL ($8.0 \times 10^9/\text{L}$), but she is neutropenic, with an absolute neutrophil count of 800/ μL ($0.80 \times 10^9/\text{L}$). Her platelet count is normal at $143 \times 10^3/\mu\text{L}$ ($143 \times 10^9/\text{L}$). A reticulocyte count is 7.55%. A blood culture revealed no growth. Immunoglobulin (Ig) levels included IgA, 131 mg/dL (1,310 mg/L) (reference range, 27–195 mg/dL [270–1,950 mg/L]); IgG, 5,265 mg/dL (52.65 g/L) (reference range, 504–1,464 mg/dL [5.04–14.64 g/L]); and IgM, 458 mg/dL (4,580 mg/L) (reference range, 24–210 mg/dL [240–2,100 mg/L]). Human immunodeficiency virus (HIV) antibody and hepatitis B surface antigen levels were normal/negative.

Ultrasonography of the abdomen revealed hepatomegaly and splenomegaly, with multiple hypoechoic lesions diffusely involving the splenic parenchyma. Computed tomography of the abdomen and pelvis showed similar findings of splenomegaly, with a small, wedge-shaped, peripheral subcapsular hypodense area in the upper pole consistent with a splenic infarct. The splenic vein was dilated in caliber (1.1 cm) and tortuous. Hepatomegaly of 11.0 cm with normal attenuation was also noted. An additional test revealed the diagnosis.

THE DEFINITIVE DIAGNOSIS

A bone marrow aspirate revealed normal erythropoiesis, myelopoiesis, megakaryopoiesis, and maturation of cells lines and an M:E ratio of 3.5:1. A careful microscopic examination of the bone marrow specimen revealed *Leishmania donovani* (LD) bodies present extracellularly and intracellularly in macrophages (Fig).

The Disease

Leishmaniasis is a vector-borne disease occurring in tropical regions where there is a high prevalence of poverty in the community. The disease can occur in multiple forms, with cutaneous involvement being the milder form, and mucosal or visceral (kala-azar) forms associated with substantial morbidity and mortality. The causative agent, *L. donovani*, exists in 2 forms: the flagellate promastigote in the sand fly vector and an aflagellate amastigote form in the human host. The promastigote is secreted into blood during a blood meal by the vector. The amastigote form exists in the phagolysosomes of the macrophages, resisting the acidic intracellular environment and multiplying

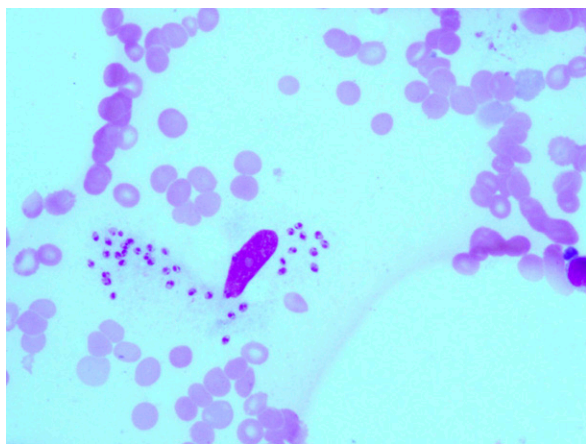


Figure. Giemsa stain showing intracellular LD bodies in the macrophages of the bone marrow aspirate (original magnification $\times 50$).

within and causing cell death. These infected macrophages help the organism evade the immune system. *L. donovani* and *Leishmania mexicana* predominantly cause visceral leishmaniasis. Rodent reservoirs maintain the zoonotic transmission, and human infection occurs when human activities bring them in contact with the reservoir and the vector. Among parasitic diseases, mortality from leishmaniasis ranks just behind that of malaria and schistosomiasis in children younger than 15 years.

The pathological hallmark of visceral leishmaniasis is hyperplasia of the reticuloendothelial system with abundant amastigotes in the histiocytes and Kupffer cells. Splenic infarcts, fatty infiltration of the liver, and erythrophagocytosis are late complications.

Visceral leishmaniasis typically affects children younger than 5 years (Table). A transient flu-like illness with few symptoms is seen in many children after the sand fly bite. The illness in this situation is self-resolving. In 25% of children, classical kala-azar then sets in with an incubation period varying from months to years. High-grade fever, marked splenomegaly and hepatomegaly, hyperpigmentation, and severe cachexia develop over 6 months after the onset of illness. Skin hyperpigmentation in patients with visceral leishmaniasis is probably due to elevated cortisol levels. Patients with visceral leishmaniasis have a high level of inflammatory markers. Stimulation of the hypothalamic-pituitary-adrenal axis due to elevated cytokines and a consequent increase in corticotropin is thought to be responsible for increased cortisol levels causing stimulation of melanocytes and hyperpigmentation. (1) Untreated, it may eventually lead to severe pancytopenia, edema, ascites, and death due to secondary bacterial infections. Leishmaniasis is also an opportunistic infection associated with HIV. Laboratory tests usually reveal severe anemia, thrombocytopenia, and leukopenia, with elevated transaminase levels and hyperglobulinemia, usually IgG. Serologic testing in visceral leishmaniasis is used as a diagnostic tool due to higher levels of antileishmanial antibodies compared with other forms of the disease. Definitive diagnosis is by demonstration of amastigotes in tissue specimens or by the culture of the organism. Amastigotes can be identified by their appearance in Giemsa-stained specimens as small eosinophilic bodies known as LD bodies (Table). Bone marrow aspirate and biopsy are commonly used for diagnosis. In difficult cases, splenic aspiration can be performed, although it carries a high risk of life-threatening bleeding. (2)(3)(4)

The Centers for Disease Control and Prevention (CDC) in the United States provides multiple resources to help

TABLE. **Leishmaniasis: A Summary**

| LEISHMANIASIS – THE DISEASE | NOTES |
|--|---|
| Clinical manifestations and laboratory characteristics | Classical visceral leishmaniasis is marked by high-grade fever, marked splenomegaly and hepatomegaly, hyperpigmentation, and severe cachexia. Severe disease is marked by pancytopenia, edema, ascites, and death. Laboratory parameters reveal severe anemia, thrombocytopenia, and leukopenia, with elevated transaminase levels and hyperglobulinemia. |
| Diagnosis | Tissue specimens—such as from skin sores (for cutaneous leishmaniasis) or from bone marrow (for visceral leishmaniasis)—are examined for the parasite for the presence of macrophages containing multiple amastigotes. |
| Treatment | Treatment with sodium stibogluconate or conventional/liposomal amphotericin B are recommended for therapy. |

with the diagnosis of leishmaniasis. These services include examination of slides, culture mediums, in vitro culture, and polymerase chain reaction for the species identification of *Leishmania*. Serologic testing with rK39 rapid test for detecting antibodies against *Leishmania* is also among the services offered. The culture tubes are mailed by the CDC with shipping labels so that clinicians can obtain specimens and send them to the CDC for laboratory/pathology evaluation/testing. (5)

Differential Diagnosis

The common differential diagnoses include malaria, typhoid, miliary tuberculosis, infectious mononucleosis, lymphoma, and leukemia. In a patient with prolonged fever, weakness, cachexia, marked splenomegaly, hepatomegaly, cytopenias, and hypergammaglobulinemia who has had potential sand fly exposure in an endemic area, visceral leishmaniasis should be suspected after the other obvious disorders have been ruled out. (6)

Management

Management of visceral leishmaniasis requires therapy with either pentavalent antimonial compounds such as sodium stibogluconate, 20 mg/kg per day intravenously or intramuscularly for 28 days, or liposomal amphotericin B, 3 mg/kg per day intravenously on days 1 through 5 and 3 mg/kg per day on days 14 and 21 (Table). Recurrence of infection is not uncommon in the immunocompromised

patient. Prevention of recurrences is by personal protection in endemic areas, vector control, and elimination of reservoirs. Currently, there are no vaccines available for visceral leishmaniasis. (7)

Patient Course

The patient was treated with liposomal amphotericin B, 3 mg/kg given for the first 5 days and on days 14 and 21. One month after therapy, at follow-up, she was afebrile, had gained 2 kg, and her pallor had resolved. Her liver and spleen were just 1.5 cm and 2.5 cm below the costal margins, respectively. The complete blood cell count was normal. However, the dark hue of her skin persisted.

Lessons for the Clinician

- Visceral leishmaniasis should be suspected in children hailing from endemic areas with prolonged fever, cachexia, and hepatosplenomegaly.
- Hyperpigmentation and hyperimmunoglobulinemia may be clinical and biochemical pointers toward the definitive diagnosis.
- The Centers for Disease Control and Prevention provides various resources for diagnosis by culture or serologic testing.

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3 Hypoglycemia in an Infant with Cholestasis

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PRESENTATION

An 8-week-old boy presents with 2 days of worsening jaundice, lethargy, and poor feeding, without fever, vomiting, or diarrhea. At term he weighed 3,400 g (43rd percentile), had hypoglycemia on day 1, and received hyperbilirubinemia phototherapy for 5 days. Physical examination is noteworthy for a lethargic and jaundiced boy weighing 4,300 g (8th percentile). The liver edge is 4 cm below the costal margin. The phallus is 1.7 × 0.7 cm, with no hypospadias, normal scrotum, and descended testes.

Initial laboratory results are as follows: blood glucose, less than 20 mg/dL (<1.11 mmol/L); total/direct bilirubin, 17.8/13.5 mg/dL (304.4/230.9 μmol/L); alanine aminotransferase/aspartate aminotransferase, 258/686 U/L (4.31/11.46 μkat/L); free thyroxine, 0.96 ng/dL (12.4 pmol/L); and thyrotropin, 4.36 μIU/mL (4.36 mIU/L).

An intravenous glucose infusion is started, and the patient is admitted to the hospital. Liver ultrasonography reveals nonspecific coarse echogenicity with gallbladder wall thickening. Liver biopsy shows marked hepatocellular cholestasis, disarray and giant cell transformation, mild portal inflammation and portal fibrosis with early bridging fibrosis, and no abnormal storage material. Testing for herpes simplex virus types 1 and 2, enterovirus, Epstein-Barr virus, cytomegalovirus, adenovirus, human immunodeficiency virus, and hepatitis viruses is negative; levels of urine succinylacetone and organic acids are normal, as are plasma galactose-1-phosphate uridylyltransferase (GALT) and acylcarnitine levels. He is tested for *ATP8B1*, *ABCB11*, *ABCB4*, and *JAG1* mutations. Hypoglycemia continues despite an intravenous glucose infusion rate of 16 mg/kg per minute. After stopping his infusion for 30 minutes, the serum glucose level is 23 mg/dL (1.3 mmol/L). Concurrent laboratory results include insulin, 0.8 μIU/mL (5.6 pmol/L); β-hydroxybutyrate, 0.1 mmol/L; free fatty acids, 0.56 mg/dL (0.02 mmol/L); and growth hormone, 1.55 ng/mL (1.55 μg/L). A low-dose cosyntropin test and brain magnetic resonance imaging (MRI) (Figure) are performed.

DISCUSSION

Differential Diagnosis

Neonatal cholestasis can be caused by obstructed bile flow or functionally impaired hepatic bile secretion secondary to structural, infectious, genetic,

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Figure. Brain magnetic resonance imaging. A. Sagittal T1-weighted image. The pituitary gland (yellow arrowhead) is diminutive in size and hypointense. A normal pituitary stalk is not visualized, indicating an ectopic neurohypophysis. B. Coronal T2-weighted image showing optic nerve hypoplasia (red arrows).

metabolic, or endocrine abnormalities. Biliary atresia is a fibro-obliterative disease of the extrahepatic biliary tree that presents with persistent jaundice, pale stools, and dark urine. Key diagnostic findings include ultrasonographic features of abnormal gallbladder size and shape, the "triangular cord" sign, poor gallbladder contractility, and absence of the common bile duct. Hepatobiliary scintigraphy shows lack of tracer excretion from liver to intestines, and liver biopsy demonstrates bile duct proliferation, a small cell infiltrate, portal fibrosis, and absence of sinusoidal fibrosis. (1)

Metabolic conditions such as galactosemia, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (fatty acid oxidation defects), and tyrosinemia type 1 can cause hypoglycemia along with cholestasis; these are usually detected by newborn screening in the United States. Galactosemia may present with vomiting and jaundice within a few days of milk ingestion. Hepatomegaly is often present, and *Escherichia coli* sepsis occurs frequently. Galactosemia is diagnosed by reduced activity of GALT. (2) Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency can present with hypoglycemia and liver disease along with elevated levels of long-chain acylcarnitines. (3) Tyrosinemia type 1, resulting from deficiency of fumaryl acetoacetate hydrolase, usually presents in infancy with severe liver dysfunction, growth failure, rickets, and renal tubular dysfunction. It is characterized by elevated tyrosine, methionine, and phenylalanine levels in plasma; increased succinylacetone levels in the blood and urine; and elevated tyrosine metabolite and δ -aminolevulinic acid levels in urine. Definitive diagnosis is made by measuring fumaryl acetoacetate hydrolyase activity in liver biopsy specimens or cultured fibroblasts. (4)

Progressive familial intrahepatic cholestasis is a group of rare autosomal recessive disorders presenting with intrahepatic cholestasis and features such as hearing loss,

diarrhea, and growth failure, and it is caused by mutations in the *ATP8B1*, *ABCB11*, or *ABCB4* gene. (5) Alagille syndrome is an autosomal dominant disorder characterized by conjugated hyperbilirubinemia owing to bile duct paucity; vertebral anomalies; congenital cardiac defects, particularly pulmonary stenosis; ophthalmologic abnormalities such as posterior embryotoxon; and characteristic facial features. Heterozygous inactivating mutations in the *JAG1* gene are found in 94% to 96% of patients. (6)

Biliary atresia was ruled out by liver ultrasonography. A viral hepatitis panel was negative; normal urine succinylacetone and organic acid levels and plasma GALT and acylcarnitine levels ruled out metabolic diagnoses. There were no mutations in the *ATP8B1*, *ABCB11*, *ABCB4*, or *JAG1* genes.

Actual Diagnosis

The infant was diagnosed as having hypopituitarism.

The Condition

The brain MRI (Figure) showed a diminutive pituitary gland (yellow arrowhead), nonvisualization of the normal pituitary stalk, and an ectopic neurohypophysis. The optic chiasm and optic nerves were markedly diminutive (red arrows), and the olfactory bulbs were absent. The cortisol level increased from 1.3 $\mu\text{g/dL}$ (36 nmol/L) to only 6 $\mu\text{g/dL}$ (166 nmol/L) (reference range, >18 $\mu\text{g/dL}$ [>497 nmol/L]) after low-dose cosyntropin stimulation.

Hypoglycemia is best evaluated with additional concurrent blood testing. Patients with hypopituitarism have low free fatty acid, lactate, insulin, cortisol, and growth hormone levels in the setting of hypoglycemia. Hypocortisolism can then be confirmed with a low-dose cosyntropin stimulation test. A brain MRI delineates anatomical causes of hypopituitarism.

A microphallus (ie, penile length <2.5 cm [7]), blunted growth hormone response to hypoglycemia, poor cortisol

response to cosyntropin, and abnormal MRI findings confirmed the diagnosis of hypopituitarism owing to septo-optic dysplasia. Septo-optic dysplasia is a rare congenital syndrome defined by the presence of at least 2 of 3 features: 1) midline forebrain defects such as absence of septum pellucidum or corpus callosum, 2) optic nerve hypoplasia, and 3) hypopituitarism. (8) Hypopituitarism should be suspected in children with hypoglycemia and midline defects such as cleft palate, midface hypoplasia, hypertelorism or hypotelorism, or central incisor; optic nerve hypoplasia presenting with wandering nystagmus or poorly reactive pupils; and microphallus. Newborn boys with hypopituitarism usually have microphallus rather than ambiguous genitalia because in the first trimester, placental human chorionic gonadotropin stimulates testosterone secretion, which promotes differentiation of the external genitalia. Testosterone secretion and consequent penile growth after the first trimester depend on luteinizing hormone secreted by the fetal pituitary gland.

Cholestasis can rarely be a feature of hypopituitarism, (9) the mechanism of which remains unclear. (10) Cortisol modulates bile flow and bile acid synthesis (11); cortisol deficiency might affect hepatic transport of bile acids across bile canaliculi. Growth hormone plays an important role in bilirubin glucuronidation and modulates the biosynthesis and secretion of bile acid in rats (12); and growth hormone deficiency can lead to abnormal biliary cell and bile duct formation. (13) Untreated hypopituitarism has also been linked to congenital hepatic fibrosis. (14) Thyroxine deficiency (not present in this patient) delays maturation of

hepatic UDP-glucuronosyltransferase activity and causes unconjugated hyperbilirubinemia. (15)

Patient Course

The patient was treated with hydrocortisone, growth hormone, and testosterone and was closely monitored for diabetes insipidus and hypothyroidism. The cholestasis resolved with growth hormone and hydrocortisone replacement.

Lessons for the Clinician

- Hypopituitarism should be suspected in children with hypoglycemia and midline defects such as cleft palate, midface hypoplasia, hypertelorism or hypotelorism, or central incisor; optic nerve hypoplasia presenting with wandering nystagmus or poorly reactive pupils; or microphallus.
- Cholestasis can be a rare presentation of hypopituitarism.
- Patients with hypoglycemia and conjugated hyperbilirubinemia should undergo endocrine evaluation for hypopituitarism.
- Cholestasis resolves with growth hormone and hydrocortisone replacement.

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Case 3: Hypoglycemia in an Infant with Cholestasis

Nivedita Patni, Kathleen Collins and Perrin White

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Index of Suspicion

3 Pain and Weakness in a 12-year-old Boy

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PRESENTATION

A 12-year-old previously healthy boy presents to his pediatrician with right-sided posterior rib pain in the context of a recent respiratory infection without associated fever. Over the next 10 days he presents another 3 times with vague symptoms of left posterior neck pain, diffuse abdominal pain, nausea, and decreased oral intake. Results of abdominal imaging, a complete blood cell count, and a comprehensive metabolic panel are normal except for increased stool burden on radiography.

The following day he presents to the emergency department, where he complains of continued abdominal pain, decreased appetite, and no urine output for 24 hours. He receives intravenous fluids and analgesics, after which his urine output, energy, and general appearance improve, and he is deemed stable for discharge. As he is leaving the emergency department, he states that he is unable to walk and is having left arm weakness and multiple episodes of urinary incontinence. Physical examination is repeated, with vital signs significant for tachycardia (heart rate of 146 beats/min) and hypertension (blood pressure of 151/83 mm Hg). He has paralysis and hypertonia of his left upper and bilateral lower extremities, decreased deep tendon reflexes throughout all extremities, pain with movement of the body, palpable stool burden, and suprapubic fullness. His sensory examination findings are normal, with no specific sensory level.

He is admitted to the hospital for further evaluation. Results of serum studies are normal. Cerebrospinal fluid (CSF) studies show an elevated white blood cell count ($112/\mu\text{L}$ [$0.1 \times 10^9/\text{L}$]) but otherwise normal findings, including levels of protein (45 mg/dL [0.45 g/L]), glucose (58 mg/dL [3.2 mmol/L]), and red blood cells ($2/\mu\text{L}$ [$0.000002 \times 10^{12}/\text{L}$]). Neuroimaging is also performed. Magnetic resonance images (MRIs) of the brain are normal. MRI of the spine (Fig) reveals the diagnosis.

DISCUSSION

The patient was diagnosed as having acute transverse myelitis (ATM), specifically, longitudinally extensive transverse myelitis (LETM), defined as a spinal cord lesion affecting 3 or more vertebral segments.

The Condition

ATM is an inflammatory spinal cord syndrome characterized by motor, sensory, and autonomic deficits. The incidence is rare, estimated to be 2 per million children per year. (1) The age distribution of pediatric patients with ATM is

AUTHOR DISCLOSURE Drs Seidenberg and Kulkarni have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

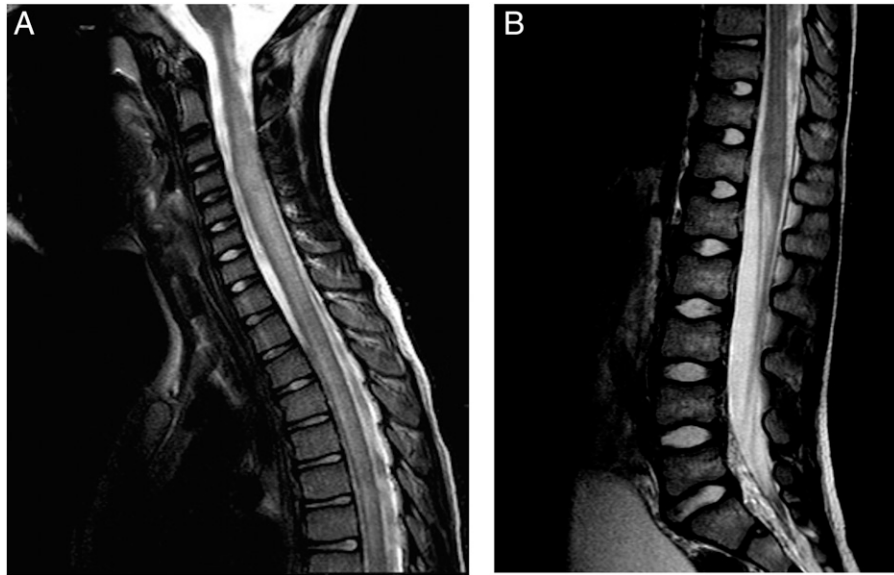


Figure. Magnetic resonance images of the spine show a hyperintense T2-weighted signal in the spinal cord from the cervicomedullary junction to the conus medullaris (20 vertebral segments). The signal abnormality involves gray and white matter of the central and posterior portions of the cord. A. Cervicomedullary junction to the eighth thoracic vertebra. B. Ninth thoracic vertebra to the conus medullaris, which ends at the first lumbar vertebra.

bimodal, with clusters at 0 to 2 and 5 to 17 years of age. (2)(3) Patients often have a preceding febrile illness. Symptoms are usually bilateral and may progress to nadir in as quickly as 4 hours or as long as 21 days. (4)

The patient discussed previously herein had an initially subtle presentation with pain, which is the presenting symptom in most children. He did have a preceding illness, but he was afebrile. His increased stool burden may have been representative of the rectal dysfunction that commonly occurs in ATM. (5) He also had bladder dysfunction causing initial urinary incontinence, subsequent bladder spasms, and then urinary retention, which is found in 95% of patients during the acute phase of this condition. (4) He never had sensory impairment with a specific sensory level, although this is identified in only approximately 60% of children. (1) His symptoms reached nadir at day 11, with a rather abrupt onset of weakness that made the diagnosis more apparent.

This patient's presentation with LETM is not uncommon, with one study citing that most pediatric patients with ATM have LETM. (6) However, his spinal cord involvement of 20 vertebral segments from the cervicomedullary junction to the conus medullaris is far more extensive than in most patients. Studies show average involvement of 6 vertebral segments in children, and lesions in adult patients extend only 1 to 3 segments. (2)(7)(8)

Differential Diagnosis

Although findings from the history and physical examination can lead to a strong presumptive diagnosis, the

differential diagnosis is broad, with ATM being a diagnosis of exclusion.

MRI is the most useful first step in evaluation because it can exclude noninflammatory diagnoses, such as compression or vascular disease. (7)(9) Cord compression from malignancy, disc herniation, or vertebral fractures can be directly visualized on MRI. Spinal cord infarction, especially when involving the anterior spinal artery, presents with sudden-onset weakness and sensory changes that may seem similar to ATM. However, spinal cord infarction can be distinguished by MRI, on which affected areas show diffusion restriction on diffusion-weighted imaging. (10) In addition, compressive and vascular etiologies typically have normal CSF findings.

If inflammatory myelopathy is visualized on MRI, it can be further divided into idiopathic and secondary ATM. Idiopathic ATM, as seen in this patient, is characterized by CSF pleocytosis and spinal cord inflammation on MRI. (7) Secondary ATM may be associated with infection, rheumatologic conditions, acute disseminated encephalomyelitis, neuromyelitis optica (NMO), or multiple sclerosis (MS). Several diagnostic studies may be obtained to help distinguish among these entities, including CSF studies (opening pressure, protein, glucose, cell count with differential count, viral studies, bacterial Gram-stain and culture, and oligoclonal bands), serum studies (complete blood cell count, blood culture, inflammatory markers, NMO antibodies, oligoclonal bands, dilute Russell viper venom time, rapid plasma reagin, Lyme disease enzyme immunoassay,

antinuclear antibody, angiotensin-converting enzyme, Sjogren syndrome antibodies, and double-stranded DNA antibody), and neuroimaging. Acute disseminated encephalomyelitis can be differentiated from idiopathic ATM in that it often includes multifocal involvement on MRI (cerebral, cerebellar, optic nerve, and spinal cord). NMO may present as ATM and is specifically associated with LETM; however, most cases are positive for serum NMO antibodies. (6) MS-associated ATM can sometimes be distinguished with MRI brain findings, and it is generally associated with recurrent episodes of ATM. Interestingly, LETM is indirectly correlated with MS. (2)(11)(12)

Another important diagnostic consideration is Guillain-Barré syndrome (GBS), which can have a similar clinical presentation to ATM. However, MRI findings in GBS have more frequent enhancement of the spinal nerve roots as opposed to the cord, as seen in ATM, and the CSF in GBS demonstrates albuminocytologic dissociation with an elevated protein level without pleocytosis. (4) This patient's presentation is also similar to that of acute flaccid myelitis given the asymmetrical spinal cord dysfunction, primary acute motor deficits, minimal sensory involvement, and CSF pleocytosis. However, MRI findings in acute flaccid myelitis exhibit specific involvement of the anterior horn gray matter of the spinal cord. (13) This is in contrast to MRI findings in ATM, which can involve both gray and white matter and portions of the spinal cord other than the anterior horn, such as the posterior and central cord, as seen in this patient.

Patient Course

The involvement of his entire spinal cord, specifically the cervical spine, put this patient at risk for respiratory decompensation, so he was transferred to the PICU. There he received 5 days of intravenous methylprednisolone, the first-line treatment for ATM. He also required plasmapheresis, which is used in corticosteroid-refractory cases. (14) During this time he continued to have dysautonomic hypertension, and he was placed on nicardipine and nitroprusside

infusions until his blood pressures normalized. Despite the extensive spinal cord involvement he did not require respiratory support. His pain was controlled with ketorolac, ibuprofen, and gabapentin. His increased stool burden was treated with a bowel regimen, and his urinary retention required an indwelling bladder catheter for 14 days. Physical and occupational therapy led to gradual improvement in his paralysis. At the time of discharge, 20 days after admission, his symptoms had fully resolved except for minimal left proximal weakness, for which he continued outpatient therapies.

Studies have shown that pediatric ATM has a better prognosis compared with adult ATM, often resolving within 3 months. In general, a poor prognosis is expected in patients younger than 3 years at onset and in those with rapid onset of severe neurologic dysfunction, such as severe muscle weakness, complete paraplegia, spinal shock, and respiratory failure. Delayed treatment, involvement of higher spinal lesions, and involvement of longer segments have also been associated with worse outcomes. (2)(8) Despite the presence of several unfavorable features, the patient described in this case had an excellent outcome, including early return of gross motor and bladder function and almost complete recovery by 2 months after discharge.

Lessons for the Clinician

- Patients with acute transverse myelitis (ATM) often present to their pediatrician's office with nonspecific symptoms of pain, urinary urgency, constipation, or weakness after a recent viral illness.
- ATM is a diagnosis of exclusion and the differential diagnosis is broad, necessitating a comprehensive evaluation, including laboratory tests and imaging.
- Diagnosis within 7 days of symptom onset is associated with better functional outcomes and overall quality of life. (2)

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3 Anisocoria in a 5-year old Girl

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PRESENTATION

A previously healthy 5-year-old girl presents to the emergency department with a chief complaint of persistent left-sided neck swelling with new-onset headache, odynophagia, and pupillary asymmetry. She has developed the left neck swelling over the course of the past month. She is initially evaluated with lateral neck ultrasonography as an outpatient; this demonstrates enlarged cervical lymph nodes without fluid collection or abscess. She completes a course of clindamycin for presumed cervical lymphadenitis and is subsequently treated with a course of amoxicillin–clavulanic acid after the first course of antibiotic agents fails to improve her symptoms. Parents state that they have not appreciated a significant change in the degree of neck swelling after the 2 antibiotic drug therapy courses, and the girl endorses a major increase in neck pain and headache last night that is unresponsive to acetaminophen or ibuprofen, both of which had previously been alleviating her pain. She is also noted to have pupillary asymmetry for the previous 2 days.

She has not had fevers, vomiting, seizures, weight loss, or changes in speech or vision. She remains at her neurologic baseline. There is no history of trauma or recent surgery. She is fully immunized and has no known allergies.

In the emergency department she is well-appearing, afebrile, and with age-appropriate vital signs. She is noted to have partial left-sided ptosis and miosis, as well as tender, palpable left-sided cervical lymphadenopathy (Fig 1).

DISCUSSION

This girl's clinical presentation is consistent with Horner syndrome, also known as oculosympathetic palsy, which is caused by a disruption of the ocular sympathetic supply to the eyelids and pupils and may occur anywhere along the 3-neuron pathway between the hypothalamus and the orbit. The etiology of Horner syndrome is varied and age dependent. (1) A retrospective review of 73 pediatric patients with Horner syndrome found that 42% were congenital in nature (including birth trauma), 42% were acquired after a surgical procedure, and 15% were acquired without surgical intervention. In the 15% of cases acquired without surgical intervention, etiologies included neuroblastoma, trauma,

AUTHOR DISCLOSURE Drs McEachern, Walz, Dantuluri, Dulek, and Betters have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Left-sided ptosis and miosis.

rhabdomyosarcoma, brainstem vascular malformation, disseminated sclerosis, and other causes not determined. (1)

Our patient's initial laboratory work revealed a white blood cell count of $9,500/\mu\text{L}$ ($9.5 \times 10^9/\text{L}$) with 68% neutrophils, a C-reactive protein level of 1.1 mg/L (10.5 nmol/L) (of note, her initial outpatient C-reactive protein level, 19 days before emergency department presentation, was 68 mg/L [647.6 nmol/L]), and an erythrocyte sedimentation rate of 23 mm/hr . She had a negative rapid mononucleosis screen. Her coagulation profile was normal. A contrasted computed tomographic scan of the head was obtained, which revealed a lobulated enhancing left cervical mass that was suspicious for a pseudoaneurysm abutting the anterior aspect of the distal left cervical internal carotid artery (ICA) at the level of the skull base. Magnetic resonance angiography of the head and neck confirmed the diagnosis of a large, partially thrombosed pseudoaneurysm of the left ICA ($1.9 \times 4.0 \times 4.0 \text{ cm}$), with moderate stenosis of the left cervical ICA along the posterolateral aspect of the pseudoaneurysm.

The Condition

Pseudoaneurysms in the ICA are rare in the pediatric population and most commonly result from traumatic injury to the carotid artery. Traumatic causes include external trauma or iatrogenic injury to the vessel during surgical procedures. Pseudoaneurysms in the ICA can also occur as a rare complication of a deep neck space infection, usually developing a few days to 2 months after the initial infection. (2) However, since the widespread use of antibiotic drugs for the treatment of otolaryngologic infections, the frequency of this complication has significantly decreased. (3)

The pathophysiology of pseudoaneurysm development after infection is not completely understood, but it is thought to be caused by the introduction of infection from pharyngeal, tonsillar, peritonsillar, or lymphatic channels. (2) A septic focus may cause adjacent arteritis and a

weakened arterial wall, leading to aneurysmal dilation. (4) Pediatric deep neck space infections are usually due to abscesses or lymphadenitis and, less commonly, bacterial endocarditis. The most common microbiological causes of cervical lymphadenitis include *Staphylococcus aureus*, streptococcal species, anaerobic organisms, and viruses (Epstein-Barr virus, cytomegalovirus, and adenovirus). (5)

Diagnosis

Clinical signs suggestive of pseudoaneurysm are Horner syndrome, paralysis of cranial nerves, a pulsating and tender neck mass, lack of resolution of lymphadenitis symptoms after antibiotic drug therapy, or stroke due to embolization of thrombus from within the pseudoaneurysm. Larger pseudoaneurysms can compress the glossopharyngeal nerve, leading to dysphagia, odynophagia, and retro-orbital headache. (6)

The diagnosis of ICA pseudoaneurysm is usually made by ultrasonography of the neck or by computed tomographic scan. Additional vascular imaging using computed tomography angiography or magnetic resonance imaging angiography is helpful to delineate the anatomy, the extent of pseudoaneurysm dilation, and its relationship to surrounding structures before initiating vascular repair.

Management

Patients with ICA pseudoaneurysm require urgent management because they are at risk for rapid decompensation secondary to hemorrhage, airway compromise, and stroke. (7) The aim of management is to restore the continuity of the artery by separating the pseudoaneurysm from the carotid circulation. Historically, this has been accomplished by surgical ligation or coil sacrifice of the vessel. However, more recently, a strategy to reestablish arterial continuity through endovascular embolization of the pseudoaneurysm and stenting of the ICA has been successful. (2)(6)(7) If

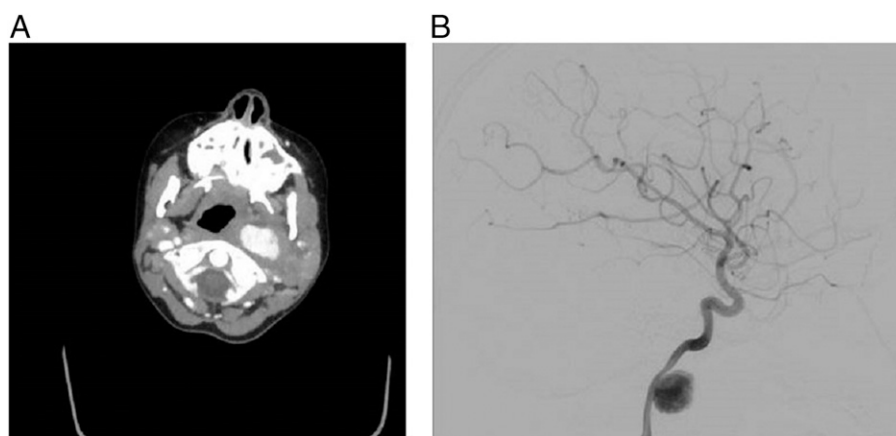


Figure 2. A. Contrast-enhanced computed tomographic scan showing a lobulated enhancing mass concerning for pseudoaneurysm at the level of the skull base. B. Angiogram showing left internal carotid artery pseudoaneurysm with moderate stenosis of the internal carotid artery.

ligation of the vessel is the planned mode of intervention, it is imperative to first ensure that there is an intact collateral blood supply to the anterior circulation.

Patient Course

Our patient was admitted to the PICU for serial neurologic checks, and both the pediatric neurosurgery and infectious disease teams were consulted. Interventional radiology-guided biopsies of a necrotic lymph node adjacent to the pseudoaneurysm as well as the left parotid gland (as the pseudoaneurysm involved its deep space) were obtained and sent for culture. Aspirin and clopidogrel prophylaxis were initiated for the pseudoaneurysm, and empirical ceftriaxone was started after lymph node biopsy.

Blood cultures and bacterial, fungal, and acid-fast bacillus cultures from the biopsied lymph node were negative. She had no evidence of acute bacterial endocarditis or endovascular infection. She had recently visited a zoo, so less common causes of lymphadenitis were considered, including *Brucella* species, *Francisella tularensis*, and *Yersinia pestis*; however, she denied contact with any animals. *Coxiella* titers were obtained given *Coxiella*'s ability to cause culture-negative endocarditis, and results were negative. Given her residence in Tennessee, *Histoplasma capsulatum* was also considered, but she had no exposure to chicken coops or construction. Tuberculosis screening was negative. Despite no known recent exposure to cats or kittens on history, she reported enjoying playing with cats. Her *Bartonella* immunoglobulin G titer was 1:256 (normal, <1:64); however, serum *Bartonella* by polymerase chain reaction was negative. Such findings were suggestive of a past or subacute infection, versus acute infection, and were consistent with her initial symptoms occurring 1 month before presentation. There are no previously published case reports of

pseudoaneurysm caused by *Bartonella* lymphadenitis; however, based on the pathophysiology of cervical ICA pseudoaneurysm secondary to deep neck infections, we believe that this underlying *Bartonella* infection was the cause of adjacent arterial inflammation, leading to pseudoaneurysm formation.

Diagnostic angiography was performed, which confirmed the ICA pseudoaneurysm (Fig 2), with significant narrowing of the ICA. Collateral blood flow to the anterior circulation was intact, and the patient underwent successful endovascular embolization of the pseudoaneurysm with reconstruction of the ICA by placement of an endovascular stent. Follow-up angiography demonstrated normal flow through the carotid artery as well as successful occlusion of the pseudoaneurysm. She was maintained on clopidogrel and aspirin therapy and was discharged on an extended course of antibacterial drug therapy with oral cefdinir. On follow-up 1 month after her procedure, she was noted to have continued Horner syndrome but resolution of neck swelling and pain. Long-term anticoagulation with aspirin and clopidogrel was continued, with plans for repeated angiography 6 months after arterial stent placement.

Lessons for the Clinician

- Consider early referral to an infectious disease specialist for evaluation of a patient with presumed lymphadenitis who is not improving with an appropriate antibiotic drug course.
- Be suspicious of internal carotid artery pseudoaneurysm in a patient with Horner syndrome.
- Patients with internal carotid artery pseudoaneurysm require urgent management because they are at risk for hemorrhage, stroke, and airway compromise.

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3 Gait Instability and Elevated Troponin Level in a 16-year-old Boy

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AUTHOR DISCLOSURE Drs Johnson and Mohan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 16-year-old white boy presents to the emergency department after a fall. He was in the bathroom when he bent over to pick up an object and lost his balance. He fell forward and chipped his front teeth on the bathtub. He admits to feeling light-headed but denies loss of consciousness. Review of systems is positive for a temperature of 100.1°F (37.8°C), headache, rhinorrhea, and chest pain with cough for the previous week.

Vital signs record a temperature of 100.0°F (37.8°C), a pulse of 85 beats/min, a respiratory rate of 18 breaths/min, and blood pressure of 130/67 mm Hg. Physical examination reveals a well-developed, well-nourished, non-toxic-appearing boy with normal cardiopulmonary examination findings. A brief neurologic examination is notable for gait instability and generalized weakness.

Laboratory evaluation shows a normal complete blood cell count and electrolyte levels. An electrocardiogram is significant for normal sinus rhythm, normal axis, ST elevation in anterior leads, and T-wave inversions in anterolateral leads (Fig). Cardiac enzymes are collected and reveal a troponin I level of 7.021 ng/mL (7.021 µg/L) (reference range, 0.00–0.06 ng/mL [0.00–0.06 µg/L]), with normal creatinine kinase and creatine kinase–MB fraction levels. His 2-hour follow-up troponin I level is 6.905 ng/mL (6.905 µg/L). The patient is transferred to a tertiary medical center with a 7-hour troponin T level of 0.053 ng/mL (0.053 µg/L) (reference range, <0.01 ng/mL [<0.01 µg/L]). An echocardiogram reveals normal left ventricle function and size with mild concentric hypertrophy, normal right ventricle size and function, and normal valves. Given his history of viral upper respiratory tract infection and elevated troponin level, there is concern for myocarditis. However, further evaluation reveals an underlying noncardiac diagnosis.

DISCUSSION

Cardiac magnetic resonance imaging was performed to assist in diagnosis. The study revealed hypertrophic cardiomyopathy with severe asymmetrical septal hypertrophy without obstruction, preserved left ventricle systolic function, and normal left ventricle chamber size. The hypertrophy pattern and late gadolinium enhancement pattern were not consistent with amyloidosis, Fabry disease, muscular dystrophy, or myocarditis.

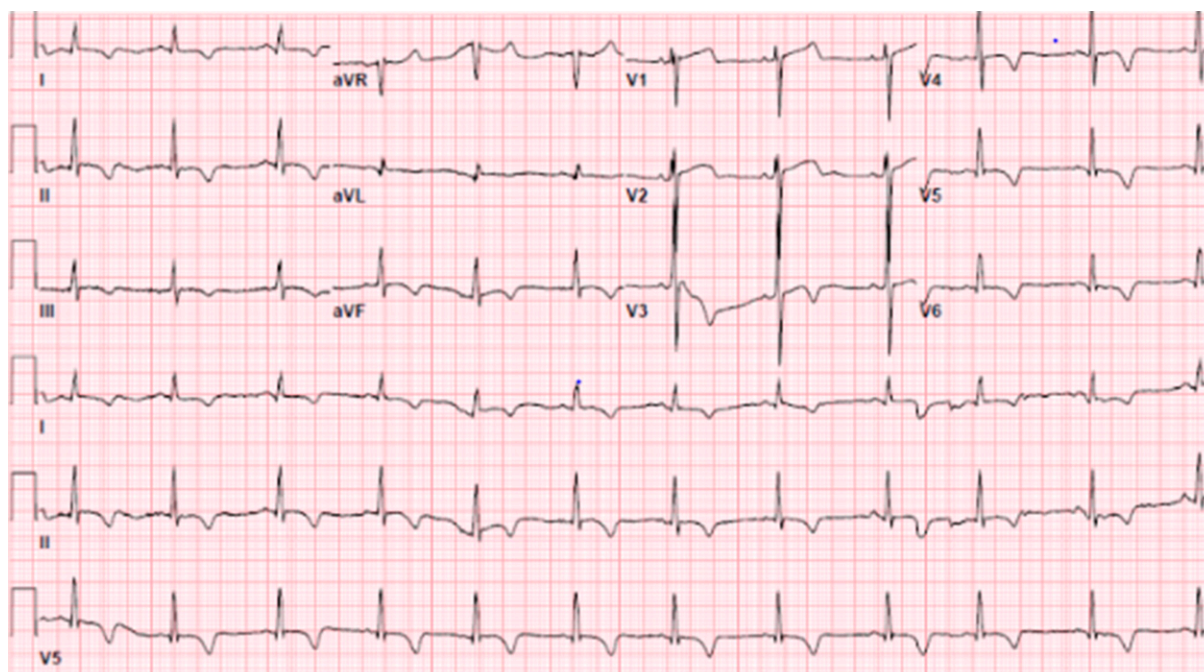


Figure. Electrocardiogram with ST elevations and T-wave inversions.

Further historical investigation revealed that the patient had a “wobbly gait” for the past 2 years. He cannot stand with his feet together and walks with a broad-based gait. He underwent an evaluation in the past that included normal electrolyte, vitamin B₁₂, creatinine kinase, and lactate levels and normal findings on magnetic resonance imaging of his brain. There was no family history of neurologic, muscular, cardiac, or genetic disorders.

A detailed neurologic examination was significant for 1+ bilateral patellar reflexes, up going plantar reflexes bilaterally, clonus at the ankles bilaterally, normal sensation, dysmetria on finger-to-nose and heel-to-shin testing, a positive Romberg sign, wide-based gait, and mild dysarthria.

Given the findings of hypertrophic cardiomyopathy, ataxia, and abnormal neurologic examination findings, there was suspicion for Friedreich ataxia (FRDA). Genetics was consulted, who agreed, and recommended repeated expansion analysis. During follow-up his genetic testing results were positive for 2 alleles with GAA trinucleotide repeat expansion: allele 1 with 1070 GAA repeats and allele 2 with 830 GAA repeats, consistent with diagnosis of FRDA.

The Condition

Friedreich ataxia is a neurodegenerative disorder and is the most common hereditary ataxia. The prevalence of this disease is approximately 1 in 50,000 individuals. It is an autosomal recessive condition with mutation in the frataxin

gene on chromosome 9q13. Almost all patients are identified as having an expansion of GAA trinucleotide repeat in intron 1 of 1 or both alleles. Deficiency in the frataxin gene can affect many different organ systems, including the central and peripheral nervous systems, heart, skeleton, or pancreas.

Clinical presentation can vary in affected individuals, pending the extent of GAA expansions. Longer expansions correlate with earlier age at onset and severity of symptoms, including extraneural involvement. Age at onset ranges from 2 years to after 25 years, but the most common age at presentation is in adolescence, with symptoms of limb ataxia, dysarthria, motor weakness, sensory loss, or eventual loss of deep tendon reflexes. Cardiomyopathy may be seen in most patients with FRDA. Patients are frequently asymptomatic, but clinical symptoms include palpitations, dyspnea, arrhythmia, or heart failure. Cardiomyopathy can be detected on ultrasonography or cardiac magnetic resonance imaging. Abnormalities on electrocardiography are commonly identified. Other conditions associated with FRDA include diabetes and spine or foot deformities, such as scoliosis or pes cavus. Not all patients will develop complications in all possible organ systems.

Evaluation and Management

Genetic testing for triplet repeat expansion in frataxin gene in 1 or both alleles confirms the diagnosis. Neuroimaging is recommended to exclude other causes for symptoms

(tumor, inflammation, infarct, hemorrhage). Nerve conduction studies typically reveal axonal sensory loss.

Management includes a multidisciplinary approach, including neurology, cardiology, physical and occupational therapy, speech therapy, orthopedics, or endocrinology based on the patient's symptoms and extent of disease. Annual follow-up by cardiology is recommended for monitoring of arrhythmia or heart failure from cardiomyopathy, which is the most common cause of death. An implantable cardioverter defibrillator is indicated for patients with presyncope, syncope, or life-threatening arrhythmias (ventricular tachycardia or fibrillation). There is no specific treatment or definitive cure for FRDA. The condition is progressive and unpredictable. Most patients are wheelchair bound approximately 15 years after onset of symptoms.

Patient Course

The patient's troponin T level peaked at 0.058 ng/mL (0.058 μ g/L) and was down trending by the time of hospital discharge; however, it did not normalize. Also, the ST-T-wave changes on his electrocardiogram never resolved. He underwent cardiac catheterization to evaluate coronary anatomy and possible myocardial bridging that would account for his persistent elevated troponin level. Cardiac catheterization did not reveal any abnormalities in his coronary arteries. His cardiac index was normal and had a mildly elevated left pulmonary capillary wedge pressure of 11 mm Hg and no signs of left ventricular outflow tract obstruction. At the time of his procedure, he also had an implantable loop

recorder placed to monitor closely for arrhythmias that may account for his symptom of dizziness. During hospitalization, he was monitored on telemetry and there was no evidence of ventricular ectopy or arrhythmias other than occasional premature atrial contractions. His respiratory panel was positive for influenza A H3, which likely accounted for his upper respiratory tract symptoms at the time of admission. He was discharged with outpatient physical therapy services and follow-up with cardiology, neurology, and genetics.

Lessons for the Clinician

- ST-T-wave abnormalities in multiple leads on an electrocardiogram in a child should prompt investigation for structural heart disease as well as possible acquired heart disease.
- Friedreich ataxia can involve nervous system, cardiac, pancreas, or skeletal defects.
- Friedreich ataxia can present with ataxia, loss of deep tendon reflexes, or up going plantar reflexes.
- Patients with hypertrophic cardiomyopathy and focal neurologic signs should raise suspicion of Friedreich ataxia and similar neuromuscular disorders.
- Prompt diagnosis of cardiomyopathy is essential as close monitoring for syncope or arrhythmias can dictate the necessity of implantable cardioverter defibrillator placement.

Suggested Readings for this article are at <http://pedsinreview.aappublications.org/content/40/2/85>.

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3 Left Eye Swelling in a 9-year-old Girl

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PRESENTATION

A 9-year-old girl presents to the emergency department for left eye proptosis and headaches. The symptoms started approximately 2 months earlier, and initially the parents decided to watch when the symptoms first developed as there was a strong family history of hyperthyroidism and proptosis. When the symptoms persisted for a month, she was brought to an optometrist, who noted conjunctival injection on examination, and was given antihistamine ophthalmic drops for a concern of allergies. The symptoms did not improve, however, and she saw her pediatrician and was subsequently sent to the emergency department for evaluation.

Initial complete blood cell count, basic metabolic panel, liver function tests, and thyroid function tests are normal. A computed tomographic (CT) scan of the head is performed and demonstrates a 4.0 × 5.5 × 4.0-cm retro-orbital enhancing mass. The patient is then transferred to a tertiary academic medical center for further evaluation and care. On admission, her vital signs consist of a temperature of 99.1°F (37.3°C), heart rate of 86 beats/min, respiratory rate of 22 breaths/min, and blood pressure of 117/58 mm Hg. On physical examination, her pupils are equal, round, and reactive to light, with intact extraocular movements and normal conjunctiva. She has left eye proptosis. An ophthalmologic evaluation is performed that shows that intraocular pressures are normal at 14 mm Hg on the right and 15 mm Hg on the left, and visual acuity is 20/20 on both sides, with sharp borders of the optic disc. Also notable is mild swelling anterior to her left ear toward her jaw that is painful on examination. Physical examination findings are otherwise normal. Further evaluation yields the diagnosis.

DISCUSSION

Patient Course

With the finding of the retro-orbital mass on the orbital CT scans, further CT scans of the neck, chest, abdomen, and pelvis were obtained and did not show any evidence of metastatic disease. Magnetic resonance imaging (MRI) of the head/orbit confirmed the mass, 5.5 × 4.5 × 4.1 cm, centered in the left sphenoid bone without orbital or intracranial involvement but extending into the infratemporal fossa with probable involvement of temporalis muscle, as well as superior rectus and left lateral rectus muscles (Fig). Open biopsy was performed by neurosurgery,

AUTHOR DISCLOSURE Drs Tseng, Gowda, and Lee have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

and initial pathologic testing yielded a preliminary diagnosis of sarcoma. After that diagnosis, a lumbar puncture evaluation and bilateral bone marrow aspiration and biopsy were performed, and neither test showed evidence of malignancy. A bone scan showed localized uptake in the left orbital ridge/temporal bone. Histopathologic analysis revealed that the specimen consisted of a monomorphic population of round to spindle-shaped cells with hyperchromatic nuclei arranged in a vague pattern of alternating cellularity. Several mitoses are noted on hematoxylin and eosin stain; however, no areas of necrosis or definitive skeletal muscle differentiation were noted in the lesional tissue. Immunohistochemical stains showed positivity for desmin and MyoD1 and were negative for myogenin. Due to the atypical nature of the appearance of the cells, the sample was sent for a second opinion and was confirmed as rhabdomyosarcoma favoring the spindle cell/sclerosing variant.

The patient was diagnosed as having retro-orbital parameningeal rhabdomyosarcoma stage 3, clinical group 3, making it an intermediate-risk disease. Although rhabdomyosarcoma confined to the orbits has a better prognosis, the tumor passing into the infratemporal fossa through the calvarium made it a parameningeal tumor with intermediate-risk categorization. She was started on chemotherapy with vincristine, dactinomycin, and cyclophosphamide and was referred for radiotherapy to start at week 4. Owing to the proximity to the brain, proton beam therapy was considered more appropriate to reduce the risk of long-term adverse

effects of cranial radiation, and she was referred to a proton beam therapy center for the same. Owing to the minimal response that she had had with the first cycle of therapy and the atypical appearance of the tumor on independent pathology review, the diagnosis was questioned and she underwent gross resection of the tumor, and the diagnosis was again confirmed to be rhabdomyosarcoma. As she recovered from surgery, she received proton beam radiation to 41.4 Gy, boosted to 50.4 Gy to the positive margins. She completed the remainder of her chemotherapy and was in remission for approximately 3 months when she had recurrent disease, which was not responsive to salvage with doxorubicin/ifosfamide or vinorelbine/cytosar/cisplatin. She had 30 Gy of whole brain radiotherapy for leptomeningeal disease and eventually died.

Differential Diagnosis

Proptosis or exophthalmos is the forward projection or displacement of the eyeball. Although exophthalmic measurements in children are based on age, the maximum asymmetry noted in the normal distribution of pediatric patients is 2 mm. (1) As such, it has been suggested that in the pediatric population, unlike adults, a lower limit than 2 mm for asymmetry should be used to prompt further evaluation. (1)

The differential diagnosis of unilateral proptosis is broad and may include trauma or infectious/inflammatory etiologies such as Graves ophthalmopathy or orbital cellulitis. (2)(3)(4) It is important to note that thyroid ophthalmopathy can present with unilateral or bilateral proptosis. (5) Other causes to consider include primary versus secondary neoplasms such as rhabdomyosarcoma, retinoblastoma, metastatic neuroblastoma, retinoblastoma, leukemia, lymphoma, optic glioma, Langerhans cell histiocytosis, dermoid cyst, or even hemangioma. Although most space-occupying orbital lesions in children are benign, malignancy remains a concern, especially in the case of additional systemic symptoms, such as fever. Rhabdomyosarcoma and other primary malignant tumors of the orbit compose a large portion of orbital malignancies in the United States, whereas in other countries secondary neoplasms are more prevalent. (2)(3)(4) As such, a wide differential should always be considered in a patient who presents with exophthalmos, especially because the findings can be subtle and affect timing of patients to seek medical care. This patient started developing symptoms 2 months before presentation, and earlier diagnosis possibly could have affected prognosis and management.

Diagnosis and Treatment

As in this case, retro-orbital rhabdomyosarcomas typically present, compared with other space-occupying lesions, with a rapid onset and progression of proptosis and globe

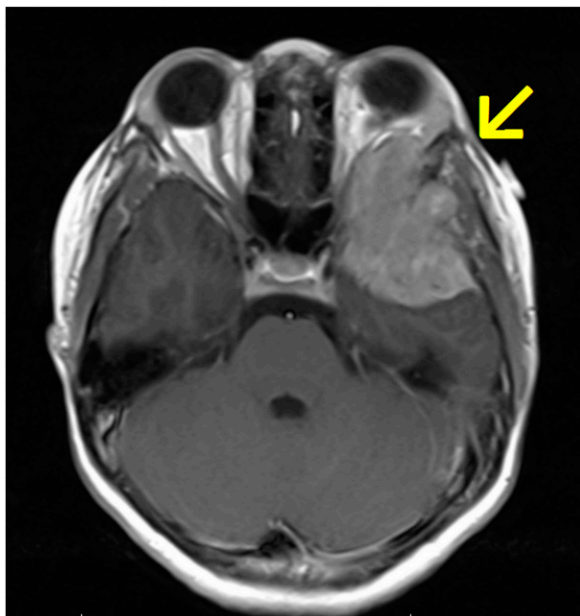


Figure. Magnetic resonance image demonstrating a soft tissue mass (yellow arrow) centered in the left sphenoid bone.

displacement. (6) Patients with orbital rhabdomyosarcoma largely present without metastatic disease. (7) Symptom manifestations depend on the origin and location of the lesion. Prognosis is generally favorable, but factors are related to age, site of origin, tumor size, resectability, presence of metastases, number of metastatic sites and tissues, staging, histopathologic subtype, and localized therapy with surgery or radiation. (8) Staging for rhabdomyosarcoma is based on pretreatment location, size, nodal involvement, and evidence of metastases, whereas grouping is based on initial surgical procedure or procedures before medical therapies and also considers lymph node involvement. (9) Both staging and grouping are used for risk stratification and to guide therapies. The treatment for orbital/parameningeal rhabdomyosarcomas is chemotherapy, often routinely including radiotherapy and surgery. (6)

Lessons for the Clinician

- The differential diagnosis for proptosis is varied; however, providers should consider neoplasm or malignancy and

use the history and physical examination to guide management.

- Orbital rhabdomyosarcoma is rapid in onset and progression, and symptom manifestation depends on the location of the lesion.
- Treatment of orbital rhabdomyosarcoma involves a combination of chemotherapy, radiotherapy, and surgery.
- Many factors, including age, site, resectability, presence of metastases, histopathology subtype, and localized treatment, affect a generally favorable prognosis.

NOTE. This case is based on a presentation by Drs Tseng, Stevens, Gowda, and Lee at Pediatric Hospital Medicine 2014, Clinical Conundrum, Lake Buena Vista, FL, Poster Session: A, Presentation Date: July 25, 2014, Poster Number: 15.

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Case 3: Left Eye Swelling in a 9-year-old Girl

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3 Prognathism in a 13-year-old Boy

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PRESENTATION

A previously healthy 13-year-old boy presents to the clinic for evaluation of prognathism. The mother reports that his jaw has grown disproportionately in the past 2 years and he is unable to close his mouth. The mother also mentions that he has been growing fast for the past 3 to 4 years and that she has frequently been buying him larger shoes and clothes. He denies headaches or blurry vision. Family history is negative for prognathism or tall stature. On examination he is found to be above the 95th percentile for height (midparental height around the 20th percentile), and his weight is at the 90th percentile. His vital signs are normal. Physical examination is pertinent only for prognathism. He is unable to completely close his mouth. He is Tanner stage 4-5.

Review of previous records shows crossing of height percentiles from the 75th to above the 95th from 9 to 11 years old, whereas his weight has been stable. Records before this age were not available because the patient is an immigrant. A bone age is read as 17 years at a chronological age of 13 years.

Hormonal evaluation reveals a growth hormone (GH) level of 7.3 ng/mL (7.3 μ g/L) (reference range, <5.0 ng/mL [<5.0 μ g/L]) and an insulinlike growth factor 1 (IGF-1) level of 725 ng/mL (95 nmol/L) (reference range, 90–589 ng/mL [12–77 nmol/L]), which are borderline high for his pubertal stage. Luteinizing hormone, follicle-stimulating hormone, and testosterone levels are late pubertal. Other pituitary hormone levels are normal. Other tests and imaging (Fig) reveal the diagnosis.

DISCUSSION

Described is a 13-year-old boy with prognathism presenting to the pediatric endocrinology clinic, being referred by his dentist. Growth chart review revealed abnormal growth velocity starting at age 9 years. On presentation, other possible etiologies for abnormal growth velocity were evaluated, including precocious puberty and hyperthyroidism. For males, precocious puberty is defined as the onset of puberty before age 9 years. Our patient may have also had a component of earlier puberty, which may have contributed to the fast growth and earlier closure of epiphysis. Hyperthyroidism was ruled out with normal thyroid function test results. Neither early puberty nor hyperthyroidism present with prognathism. He did not have any other facial dysmorphic features or neurocognitive problems to suspect any syndromic or chromosomal cause of tall stature, including Soto, Klinefelter, or XYY syndrome. There were no skin findings to support a diagnosis of neurofibromatosis or McCune-Albright syndrome.

AUTHOR DISCLOSURE Drs Chan and Minutti have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. Dr Chan's current affiliation is Medical College of Georgia at Augusta University, Augusta, GA.

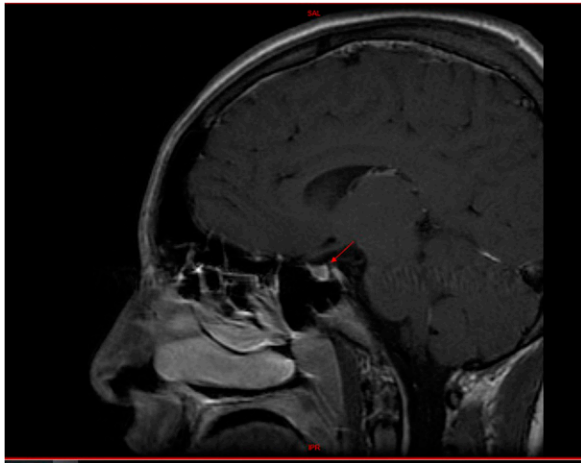


Figure. Magnetic resonance image showing pituitary adenoma.

Laboratory tests showed GH levels above limits of normal, IGF-1 levels were borderline high for pubertal status, and a GH suppression test was abnormal (GH level after oral glucose load of 1.12 ng/mL [1.12 μ g/L], normal is <0.3 ng/mL [<0.3 μ g/L]). The clinical picture, in conjunction with the test results, suggests a diagnosis of gigantism. Magnetic resonance imaging with contrast reveals a pituitary adenoma. No other testing was performed for the diagnosis of early puberty after finding the pituitary adenoma.

His Tanner stage and pubertal hormones were compatible with a postpubertal stage at age 13 years, so he may have had a component of early puberty, also caused by his pituitary adenoma. This may have contributed to the advancement of his bone age.

Pituitary gigantism results from persistent increased secretion of GH. This excess will stimulate the secretion of IGF-1, causing clinical manifestations. Patients with excess GH secretion before fusion of growth plates will present with increased growth velocity with concurrent rapid weight gain, growth of hands and feet, frontal bossing, and macroglossia. Research by Rostomyan et al on an international collaborative study of 208 patients shows that the most frequent initial clinical sign is increased growth velocity, which is observed in 75% of patients. This is followed by acral enlargement in 37% of patients. Acromegaly is due to excessive GH production after epiphyseal closure. Manifestations of acromegaly include increased skull circumference, broadening of the nose, enlargement of the tongue, coarsening of the facial features, excessive mandibular growth causing prognathism, separation of the teeth, thickening of the fingers and toes, and dorsal kyphosis. The average time of presentation is late

prepubertal childhood or early adolescence, with a median age of 13 years. The GH and IGF-1 levels are clues for diagnosis, but a normal test does not rule out the condition. A glucose suppression test should be performed to confirm excess GH production. Ingestion of 1.75 g/kg of glucose (maximum of 75 g) causes insulin secretion, leading to suppression of IGF binding protein 1. This causes an acute increase in free IGF-1 levels. The increased free IGF-1 suppresses GH secretion within 30 to 90 minutes. A GH nadir of less than or equal to 0.3 to 1.0 ng/mL (<0.3–1.0 μ g/L) is considered normal. Confirmation of this diagnosis warrants imaging to evaluate for the presence of an intracranial mass. Depending on the size of the pituitary mass, headaches and visual changes can also be present. Overproduction of GH can be an isolated abnormality or part of a syndrome, including McCune-Albright syndrome and multiple endocrine neoplasia type 1. History and physical examination is very important. Surgical removal of the tumor is the treatment of choice but is not always curative. Physical changes such as bone enlargement that occur due to excess GH are irreversible and require surgical correction. Surgery should be postponed until GH and IGF-1 levels normalize.

After transsphenoidal resection of the pituitary adenoma, the patient was followed to rule out recurrence of pituitary adenoma or hypopituitarism. On follow-up, no further mandible growth was reported, and all laboratory evaluations were normal. Repeated magnetic resonance imaging showed no evidence of a pituitary mass. He was then referred for jaw reconstruction.

Lessons for the Clinician

- Clinical presentation of children with pituitary gigantism varies.
- Children who present with increased growth velocity and acral enlargement or broadening of facial features warrant investigation of growth hormone excess.

NOTE. This case is based on a presentation by Dr Carla Minutti at the European Society for Paediatric Endocrinology yearly meeting in Paris, France, on September 10–12, 2016. Poster session: Syndromes: Mechanisms and Management; Poster number: P2-877; Session date: September 12, 2016; Session time: 13:45–14:45 PM. Portions of this case have been previously published as part of the aforementioned conference presentation.

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Case 3: Prognathism in a 13-year-old Boy

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Index of Suspicion

3 Two Preschoolers with Fever

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CASE 1

A 15-month-old Boy with Fever, Refusal to Bear Weight, and Small Foot Lesions

Presentation

A 15-month-old boy presents to the emergency department in May with a 3-day history of fever, irritability, poor oral intake, and refusal to bear weight. He has no history of cough, vomiting, diarrhea, or rash other than a lesion on the sole of his left foot, where his mother reports there was a possible insect bite 1 week earlier. He was previously healthy, and his immunizations are up to date. He lives in a rural area of southern New Jersey. The family denies recent travel or ingestion of raw foods or milk. He had visited a farm 2 weeks earlier but denies direct contact with farm animals. He has had contact with a 2-year-old cat but denies bites or scratches.

On examination he is ill appearing. Vital signs reveal a temperature of 103.5°F (39.7°C) and tachycardia. He is irritable but does not have meningismus. His abdominal examination findings are normal. He has no appreciable lymphadenopathy. On extremity examination his strength is normal. He has two 2-mm, erythematous, raised, tender papules on the plantar aspect of his left foot, but otherwise no specific tenderness to palpation or swelling along his lower extremities. Due to fever and irritability, he underwent a full sepsis evaluation, including lumbar puncture, blood culture, and urine culture. Initial cerebrospinal fluid cell count was normal. His laboratory values are notable for a white blood cell (WBC) count of $15,700 \times 10^3/\mu\text{L}$ ($15.7 \times 10^9/\text{L}$), with 60% neutrophils, 31% lymphocytes, and 6% bands; C-reactive protein (CRP), 115 mg/L (1,095 nmol/L); and erythrocyte sedimentation rate, 31 mm/hr. He receives a normal saline bolus and is admitted to the inpatient pediatrics ward without empirical antibiotics.

DISCUSSION

While hospitalized, he continues to have daily fever, with a temperature ranging from 101.8°F to 104.5°F (38.8°C–40.3°C). His irritability and oral intake improve, but he still refuses to bear weight. His WBC count peaks at $24,000/\mu\text{L}$ ($24.0 \times 10^9/\text{L}$), but his CRP level and ESR trend downward. His cultures from blood, urine, and CSF samples are negative. He tests positive for

AUTHOR DISCLOSURE Drs Mittal, Marlowe, Elliott, Gifford, Ritenour, and Topol have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

human rhinovirus/enterovirus by polymerase chain reaction (PCR) of respiratory secretions. He tests negative for Epstein-Barr virus, cytomegalovirus, and *Bartonella* by serologic testing. Abdominal ultrasonography is performed to evaluate nonspecific tenderness on examination and reveals mild splenomegaly (9.4 cm) and trace perihepatic fluid.

Owing to his persistent refusal to bear weight on the left lower extremity, imaging is obtained. He has normal ultrasonography findings of the left hip and normal plain radiography findings of the left femur, tibia, and fibula. Magnetic resonance imaging findings of the left lower extremity are negative other than an incidental finding of mild left inguinal lymphadenitis. This soon becomes clinically apparent, and he is started on clindamycin intravenously.

Through the hospitalization, his examination shows continued evolution of foot lesions. The 2 papules progress into coalescing vesiculopustules, the larger one measuring 7.5 mm, surrounded by pinpoint vesicles (Fig 1). Serial cultures are obtained and are pending. Owing to persistent fever, he is transferred to a tertiary care pediatric hospital on day 4 for a pediatric infectious disease consultation, where results of an extended viral PCR panel of a stool sample are negative. He also tests negative for cytomegalovirus, human herpesvirus 6, adenovirus, enterovirus, and parvovirus by PCR of a blood sample. Despite



Figure 1. Case 1: papulopustular lesions on the left foot.

persistent fever, his behavior and disposition improve, and he is discharged with a diagnosis of presumed viral infection.

After discharge, the second wound culture grows a gram-negative coccobacilli suspicious for *Francisella tularensis*, which is confirmed by the state laboratory using PCR. He is treated with ciprofloxacin. His fever resolves, and he makes a full recovery.

CASE 2

A 4-year-old with Fever, Cervical Lymphadenopathy, and Pulmonary Nodules

Presentation

A previously healthy 4-year-old girl presents in June with a 2-week history of persistent high temperatures up to 102.9°F (39.4°C) and worsening right cervical lymphadenopathy. Her mother had removed a tick from her scalp 2 days before the onset of her symptoms, and she has developed an enlarging pustuloulcerative lesion at that site.

She denies cough, weight loss, and night sweats. There is no history of international travel, exposure to tuberculosis, bites or scratches by kittens, or other animal exposure. She has no significant medical or surgical history, and her family and social history are unremarkable.

Since the onset of fever she has received 2 days of amoxicillin for possible otitis media, followed by 2 days of intravenous clindamycin for suspected cellulitis, and she has completed 9 of 14 days of amoxicillin/clavulanic acid for suspected Lyme disease.

Despite this, her fever and scalp lesion have persisted and her neck mass has increased considerably in size. She is seen at an outside emergency department, diagnosed as having cervical adenitis, and admitted to our community hospital on intravenous clindamycin.

Physical examination reveals a temperature of 101.5°F (38.6°C) but otherwise stable vital signs. She appears well but seems to be in pain from her neck mass. Examination of the scalp reveals a 1 × 1-cm shallow ulcer covered with dried pus and with surrounding erythema (Fig 2). She has a large 5 × 8-cm mass in her right neck extending from behind the ear to the lower neck; it is erythematous, multilobulated, firm, and tender, with mild fluctuation (Fig 3). Her neck movements are limited secondary to pain. The remainder of the examination findings are normal. Specifically, there are no other enlarged lymph nodes, her chest is clear, and there is no hepatosplenomegaly.



Figure 2. Case 2: pustular ulcerative lesion on the right scalp at the site of a tick bite.



Figure 3. Case 2: 5 × 8-cm ipsilateral, right cervical and postauricular lymphadenitis.

DISCUSSION

A complete blood cell count shows a high WBC count at $17,300/\mu\text{L}$ ($17.3 \times 10^9/\text{L}$), with 71% neutrophils, 20% lymphocytes, and 7% monocytes. She has an elevated CRP level of 92 mg/L (876 mmol/L) and an ESR of 76 mm/hr. A computed tomographic scan of her neck reveals multiple phlegmonous lymph nodes as well as 2 small (3- to 4-mm) pulmonary nodules in the lung apices (Fig 4). Chest radiography is negative, with no apparent nodules and no hilar lymphadenopathy.

Ulceroglandular tularemia is suspected based on the course of her illness over the preceding 2 weeks with a nonhealing scalp lesion after tick bite, persistent fever, worsening regional suppurative lymphadenopathy, and poor response to clindamycin and amoxicillin/clavulanic acid. Pulmonary nodules were thought to have resulted from transient bacteremia and miliary spread to the lungs.

Blood culture, wound culture, and tularemia antibodies are sent for testing. The laboratory and the Department of Health are notified about the possibility of tularemia, and the patient is started on intravenous gentamicin. *Bartonella* titers are also sent for testing, and a purified protein derivative test is performed.

Her fever resolved within 2 days, but she required incision and drainage for suppurating lymph nodes. She was discharged 3 days later on oral ciprofloxacin.

Tularemia antibody titers were consistent with a diagnosis of tularemia (1:2,560; reference range, <1:20). Blood and wound cultures were negative. Results of purified protein derivative and *Bartonella* testing were also negative. Lymph node pathologic analysis showed epithelioid cell granulomas and caseous necrosis consistent with tularemia. Lymph node cultures including acid-fast bacillus were negative.

THE CONDITION

Tularemia (deerfly fever, rabbit fever) is caused by *F tularensis*, an aerobic, fastidious, gram-negative coccobacillus. The bacterium was first discovered in 1906 in Tulare County in California and was named *Bacterium tularensis* after the county. Human disease (deerfly fever) was first described in 1911, but it was not until 1924 that a US public health physician, Dr Edward Francis, linked the bacterium to the disease. The bacterium was renamed *Francisella tularensis* in his honor. There are 4 known subspecies, with different levels of pathogenicity and presentations. The subspecies *tularensis*, found in the United States, is one of the most

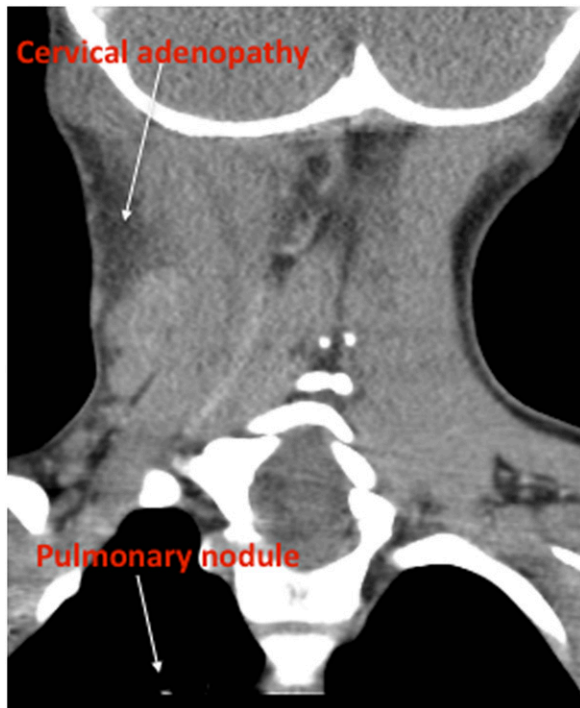


Figure 4. Case 2: computed tomographic scan of the neck showing extensive suppurative right cervical adenitis and a pulmonary nodule in the apex of the right lung.

pathogenic organisms, with potential for use as a bioterrorism agent.

Tularemia affects many animals, including rabbits, squirrels, muskrats, beavers, and voles, which act as a reservoir. Transmission can occur from animal contact (handling, ingestion, bite), from arthropod bites, or through contaminated water and soil; however, insect bite is the most common mode of transmission in children. Ticks (wood tick, dog tick, lone star tick) are the most common vector in most of the United States, but deerflies, horseflies, mosquitoes, fleas, and lice can also transmit the disease. Transovarian transmission in ticks allows for human transmission without the need for an infected-animal reservoir. Person-to-person spread does not occur.

Tularemia is rare in the United States, with approximately 100 to 200 reported cases per year since the early 1990s. Most cases occur in the south-central states, but there has been a recent shift to the north.

Tularemia is rare in New Jersey, with only 8 reported cases between 2001 and 2015, with the greatest incidence in June and July. However, our 2 cases represent a significant surge, with 4 reported cases in the first 8 months in 2016. The NJ Department of Health speculates that the increased incidence in New Jersey is a result of local infected rabbit populations, which are spreading the infection

to ticks. Our first case may have been from the child injuring the sole of his foot from the remains of an infected rabbit. The second case likely occurred from a tick bite on the scalp.

The incubation period for tularemia is 3 to 5 days, with a range of 1 to 21 days. Once inoculated into the skin, the organism multiplies at the site of inoculation, spreads to regional lymph nodes, and may spread further via the lymphohematogenous route.

Childhood tularemia most commonly presents in children aged 5 to 10 years, with glandular tularemia marked by fever and lymphadenitis, mostly in the cervical or occipital region. The second most common presentation is ulceroglandular, which in addition to the symptoms in the glandular form presents with an erythematous papuloulcerative lesion with a central eschar at the site of the bite. Hematogenous spread can cause secondary pneumonia or miliary disease, which can be asymptomatic. Other rare forms include primary pneumonic, typhoidal (fever), oculoglandular (conjunctivitis), and oropharyngeal disease.

Childhood tularemia often presents as lymph node suppuration, with 20% of children needing incision and drainage. Rare presentations include sepsis, renal failure, rhabdomyolysis, mastoiditis, meningitis, empyema, hepatitis, osteomyelitis, peritonitis, endocarditis, and pericarditis.

Presumptive diagnosis is by detection of elevated serum antibody titers to *F tularensis* antigen (without documented minimum 4-fold change) or detection of *F tularensis* in a clinical specimen by fluorescent assay.

Confirmation requires isolation of *F tularensis*. Isolates are confirmed by PCR assays available from state laboratories. PCR can also be used on biological specimens but is not as sensitive. A 4-fold change in serum antibody titers can also be used to confirm the diagnosis.

Recommended treatments for children include intravenous gentamicin for 7 days or oral ciprofloxacin for 10 to 14 days for moderate disease, with longer therapies for serious infection.

The differential diagnosis of ulceroglandular tularemia includes rickettsial diseases, cat-scratch disease, and *Spirillum minus* (rat bite fever), among others.

Lessons for the Clinician

- Tularemia should be considered in the differential diagnosis of lymphadenopathy, especially in the summer months, when there is increased risk of tick bites.
- Inquire about tick bites and examine closely for hidden lesions on the scalp in all children with acute cervical lymphadenitis.

- Test for tularemia if lymphadenitis is not improving with appropriate antistaphylococcal coverage.
- Tularemia can be transmitted from a cat scratch or bite and should be considered in the differential diagnosis of cat-scratch disease.

- Avoid tick bites and contact with sick and dead animals (rabbits, squirrels, etc)

Suggested Readings for this article are at <http://pedsinreview.aappublications.org/content/40/4/197>.

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Nontuberculous Mycobacterial Infections in Children: 1. D; 2. A; 3. C; 4. D; 5. B.

Case 3: Two Preschoolers with Fever

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and Howard Topol

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4

Chronic and Progressive Muscle Weakness in a 9-year-old Girl

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PRESENTATION

A 9-year-old previously healthy girl presents to the clinic with complaints of progressive weakness during the past 2 years. She recently quit her swim and dance teams because her weakness is so severe that she cannot keep up with her peers. She noticed more difficulty with tasks such as opening jars and exhibited decreased endurance for all physical activity. Other notable symptoms include difficulty initiating and sustaining sleep, as well as weight loss despite increasing calorie consumption. She denies diplopia, muscle twitching or cramping, numbness or tingling in her limbs, bowel or bladder changes, or difficulties with swallowing. She does not have a family history of neuromuscular disease.

Vital signs reveal slight tachycardia. Examination reveals a thin young girl in no apparent distress. She has no obvious facial or shoulder girdle muscle wasting. Strength is diffusely 4/5 throughout her upper and lower limbs. Coordination and motor planning tasks are within normal limits. A Gowers sign is negative. Her gait is essentially normal, with a small increase in foot slap during initial contact after prolonged walking.

Evaluation includes screening laboratory values of creatine kinase, complete blood cell count, thyrotropin, and free thyroxine (T₄). All laboratory values return normal except for thyrotropin (which was undetectable) and free T₄ (which was 15.1 ng/dL [194.3 pmol/L]).

DISCUSSION

Clinical Assessment of Muscle Weakness

The assessment of weakness in the child can be daunting because the differential diagnosis is broad. However, a thorough history, physical examination, and basic laboratory work can help to narrow the list of potential diagnoses. Although some diagnoses require nuanced and specialty-level neuromuscular disease knowledge, pediatricians can make significant progress toward establishing an etiology before neuromuscular specialist referral by following these general guidelines.

History

Information obtained through history is extremely valuable. The sex of the child, although obvious, can help eliminate fairly common and potentially devastating causes of weakness, such as Duchenne, Becker, and Emery-Dreifuss muscular

AUTHOR DISCLOSURE Drs A. Powell and T. Powell have disclosed no financial relationships relevant to this article. Dr Wilson has disclosed that she has a research grant from the Centers for Disease Control and Prevention (CDC) for a multicenter database related to spina bifida. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

dystrophies because these are X-linked muscle disorders. A detailed timeline of the weakness is also very helpful. Congenital myopathies and most spinal muscular atrophies can almost be ruled out in children who do not present with weakness until late childhood and who meet their gross motor milestones on time. A family history of muscle disease can be telling because myotonic dystrophy (the most common neuromuscular disorder) and fascioscapulohumeral muscular dystrophy are autosomal dominant. Many limb girdle muscular dystrophies, hereditary sensory motor neuropathies (Charcot-Marie-Tooth [CMT]), and mitochondrial myopathies can be autosomal dominant as well.

A detailed symptom history is also important. Exercise intolerance, cramping, and myalgias may be indicative of difficulties with glycogenesis, such as acid maltase deficiency (Pompe disease) or defective lipid metabolism. Myophosphorylase kinase deficiency (McArdle disease) may present similarly but with myoglobinuria. A relapsing-remitting course with worsening symptoms toward the end of the day would support a diagnosis of autoimmune myasthenia gravis. Symptoms of neuropathic pain or sensory loss may represent a generalized neuropathy, such as CMT. Weight changes, sleep disturbances, and skin changes may increase suspicion of a thyroid disorder.

Physical Examination

Physical examination is similarly helpful. Facial weakness is characteristic of myotonic dystrophy or fascioscapulohumeral muscular dystrophy. Ataxia on examination indicates ataxic neuromuscular disorders such as Friedreich ataxia. Cavus foot deformities and hammer toes in conjunction with decreased sensation and strength distally suggest CMT or other neuropathy. Grip or percussion myotonia is pathognomonic for myotonic dystrophy. A Gowers sign, although nonspecific, is informative regarding the severity of pelvic girdle weakness and can be seen in dystrophinopathies such as Duchenne, Becker, and limb girdle muscular dystrophies.

Laboratory Screening

A few screening laboratory values will narrow the differential diagnosis of a child presenting with weakness. Creatine kinase is probably the single most important muscle screen. Duchenne, Becker, most limb girdle, and some congenital muscular dystrophies can be effectively ruled out with normal creatine kinase levels. In addition, myotonic dystrophy and some metabolic myopathies can present with elevated creatine kinase levels. Weakness and fatigue may be difficult for children to distinguish in history, so a basic complete blood cell count can be helpful in screening for anemia. Finally, thyroid screening should be ordered on any

child who presents with new weakness because thyroid dysfunction is a treatable cause of weakness. Genetic testing, electromyography, muscle imaging, and muscle biopsy are further diagnostics for a neuromuscular specialist to run.

Case Diagnosis and Treatment

The low thyrotropin and elevated T₄ levels in our patient raised clinical suspicion for a hyperthyroid condition. The diagnosis was supported by a clinical history of sleep disturbance and weight loss. The cause of hyperthyroid is further elucidated in additional laboratory evaluation, which included thyrotropin receptor, thyroid-stimulating immunoglobulin, and thyroperoxidase autoantibodies. In our patient, all of these assays returned positive, confirming the diagnosis of Graves disease. Graves is an autoimmune disorder in which thyrotropin receptor autoantibodies stimulate the thyroid gland to produce both T₄ and triiodothyronine (T₃), with systemic suppression of thyrotropin production via feedback.

Graves disease accounts for 95% of all cases of hyperthyroidism in children and adolescents, with an overall prevalence of approximately 1 in 5,000. Girls are 5 times more likely to carry the diagnosis than boys. Common symptoms of Graves disease include accelerated growth, stare and lid lag, ophthalmopathy with resulting extraocular muscle weakness, goiter, tachycardia, mitral valve prolapse, tremor, benign intracranial hypertension, hyperhidrosis, and weight stagnation or loss by increased calorogenesis. Children may also suffer in school, likely from a combination of decreased attention, hyperactivity, and poor sleep patterns. Finally, weakness of proximal muscles as well as decreased muscle contraction efficiency and fatigue can be presenting symptoms, as was the case with our patient.

The goal of treatment in Graves disease is to obtain a euthyroid state. Thionamide drugs such as methimazole can be used to inhibit thyroid hormone synthesis. Treatment for at least 18 months has demonstrated some benefit regarding remission. Thyrotropin levels that remain suppressed despite treatment indicate a higher likelihood of relapse. Radioiodine (iodine 131) decreases thyroid hormone production but is not commonly used in children given the radiation exposure risk. Our patient underwent treatment with methimazole 15 mg twice daily with T₃ and free T₄, and we monitored her thyrotropin levels monthly; the methimazole dose was eventually lowered to 5 mg twice daily.

After 2 months her thyroid function returned to normal levels. At 3-month follow-up she reported improvement in muscle weakness to the point that she felt confident in rejoining her dance team.

Lessons for the Clinician

- The differential diagnosis for weakness in a child may be broad but can be significantly narrowed with a thorough history and physical examination.
- Simple screening laboratory tests, such as creatine kinase, complete blood cell count, and thyroid studies, represent a low-cost, high-yield evaluation.
- Although rare, thyroid conditions can contribute to weakness in children and should be investigated.
- Referral to a neuromuscular specialist should be considered after first-line history, physical examination, and laboratory screening are conducted.

Suggested Readings for this article are at <http://pedsinreview.aappublications.org/content/40/12/647>.

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Case 4: Chronic and Progressive Muscle Weakness in a 9-year-old Girl

Aaron Powell, Pamela Wilson and Tamara Powell

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Case 4: Chronic and Progressive Muscle Weakness in a 9-year-old Girl

Aaron Powell, Pamela Wilson and Tamara Powell

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4 Large-Volume Hematemesis in a 16-year-old Boy

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PRESENTATION

A 16-year-old Hispanic boy presents to our emergency department (ED) with recurrent episodes of bloody emesis. Two other episodes occurred 1 and 3 months before the current presentation. The volume of bloody emesis during these episodes was small and without associated hemodynamic instability. However, the family did not have any health insurance secondary to absence of a legal immigration status, declined further evaluation, and missed their follow-up appointments. In the ED, the patient is tachycardic and diaphoretic with a supine heart rate of 140 beats/min and blood pressure of 78/50 mm Hg, a respiratory rate of 25 breaths/min, and oxygen saturation of 95% on room air. He experiences a brief syncopal episode on sitting upright and is subsequently administered 2 normal saline boluses (1 L each). His initial hemoglobin level is noted to be 8 g/dL (80 g/L), and transfusion of 1 U of packed red blood cells is initiated. Initial laboratory values are noted as follows: serum sodium, 137 mEq/L (137 mmol/L); potassium, 4.2 mEq/L (4.2 mmol/L), chloride, 102 mEq/L (102 mmol/L), bicarbonate, 24 mEq/L (24 mmol/L), blood urea nitrogen, 26 mg/dL (9.3 mmol/L), creatinine, 0.68 mg/dL (51.9 μ mol/L), albumin, 3.5 g/dL (35 g/L), aspartate aminotransferase, 30 U/L (0.50 μ kat/L), alanine aminotransferase, 37 U/L (0.62 μ kat/L), total bilirubin, 0.5 mg/dL (8.6 μ mol/L), ammonia, 38 μ g/dL (27.1 μ mol/L), prothrombin time, 16.7 seconds, and activated partial thromboplastin time, 25 seconds. A nasogastric tube is inserted, and cold-water lavage is instilled, which causes the patient to have a large-volume bloody emesis. On arrival at the PICU, he is started on pantoprazole and octreotide drips, and the pediatric surgery and gastroenterology services are consulted.

His bleeding is not controlled while receiving pantoprazole and octreotide drips for an hour. Owing to hypovolemic hemorrhagic shock, he is electively intubated, and emergency bedside esophagogastroduodenoscopy (EGD) is performed. EGD reveals extensive gastroesophageal varices with a positive nipple sign suggestive of recent bleeding (Figs 1 and 2). A total of 6 esophageal varices are banded, and bleeding is temporarily stopped. Within 30 minutes of banding, the

AUTHOR DISCLOSURE Drs Dasgupta, Olaloye, Pierce, and Glaser have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

patient has another large-volume bloody emesis. EGD is again performed and reveals active bleeding from an un-banded varix at the gastroesophageal junction. His hypovolemic hemorrhagic shock subsequently worsens, requiring initiation of an institutionally based massive transfusion protocol. He receives 8 U of packed red blood cells, 6 U of fresh frozen plasma, 6 U of platelets, 4 U of cryoprecipitate, and 1 mg of factor VII. Upper gastrointestinal bleeding is eventually controlled with placement of a Sengstaken-Blakemore tube under tension with balloon inflation, allowing for tamponade of gastric and esophageal varices. Abdominal ultrasonography demonstrates absent flow in the portal vein, and additional computed tomography (CT) reveals the diagnosis.

DISCUSSION

A CT scan of the abdomen demonstrated cavernous transformation of the portal vein, prominent gastroesophageal varices, and splenomegaly measuring 17.1 cm (Fig 3). Radiographic and clinical findings were suggestive of chronic occlusion of the portal vein. There is no known family history of clotting disorders, and he did not have any stigmata of chronic liver disease or ascites on physical examination; also, he never had an umbilical line placed. On day 5 of hospitalization, surgical repair with a meso-Rex bypass procedure is attempted. However, due to the small caliber of intrahepatic portal vein branches, a distal splenorenal shunt is successfully performed instead. Subsequent CT shows a decrease in size of the gastroesophageal varices. Evaluation for

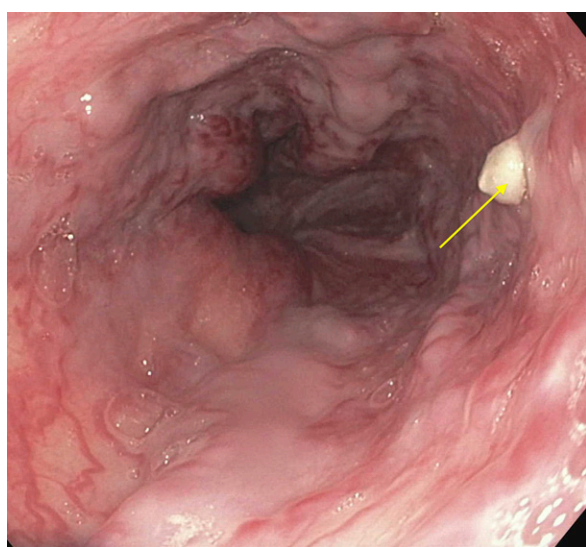


Figure 1. Esophagogastroduodenoscopy demonstrating large esophageal varices with a positive nipple sign (arrow) suggestive of recent bleeding.

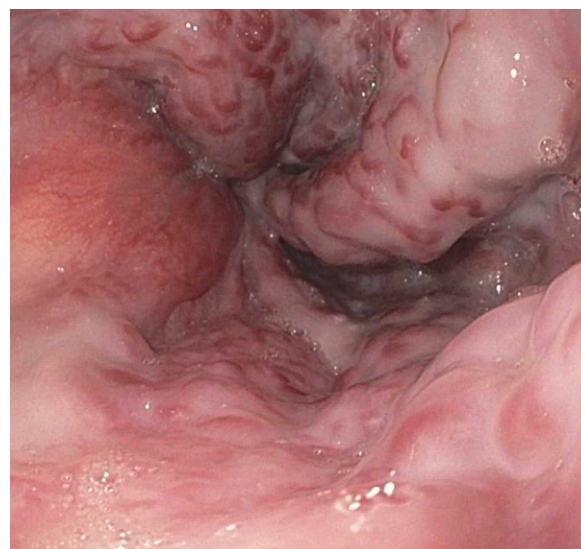


Figure 2. Esophagogastroduodenoscopy demonstrating large esophageal varices.

hypercoagulability disorders reveals elevated levels of immunoglobulin (Ig) M, IgG, and IgA anti- β_2 glycoprotein I antibody (26.7, 56.8, and 45.8 SU, respectively; reference range, 0–20 SU), suggestive of antiphospholipid antibody syndrome (APS). He is discharged on hospital day 14 with low-dose aspirin and close outpatient follow-up. A liver biopsy is pending at the time of discharge.

THE CONDITION

Upper gastrointestinal bleeding may manifest as hematemesis, melena, or, rarely, hematochezia and has a broad

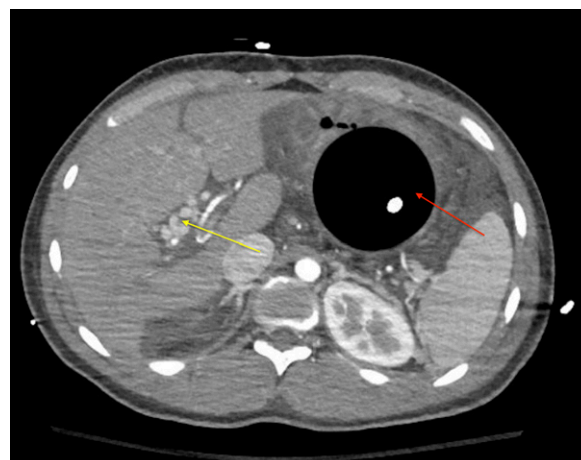


Figure 3. Computed tomographic scan of the abdomen demonstrating cavernous transformation of the portal vein with collateral formation (yellow arrow) and the presence of a Sengstaken-Blakemore tube (red arrow).

TABLE. Common Conditions Leading to Extrahepatic Portal Vein Obstruction and Their Pathophysiologic Mechanisms

| PATHOPHYSIOLOGIC MECHANISM | CONDITION |
|-----------------------------------|---|
| Portal flow obstruction | Cirrhosis Tumor obstructing portal vein Budd-Chiari syndrome |
| Hypercoagulable states | Inherited thrombophilia Factor V Leiden Prothrombin gene mutation Protein C and S deficiency Antithrombin III deficiency <i>MTHFR</i> gene mutation Acquired thrombophilia Myeloproliferative disorder Antiphospholipid syndrome Hyperhomocysteinemia Paroxysmal nocturnal hemoglobinuria Pregnancy/puerperium Oral contraceptives Sepsis Cirrhosis |
| Vascular damage | Trauma Surgery Liver transplant Invasive procedures Infections |
| Malignancy | Hepatocellular carcinoma Cholangiocarcinoma |

differential diagnosis. (1) The causes of upper gastrointestinal bleeding vary by age. The most common cause in the neonatal age group is swallowed maternal blood followed by gastritis, and peptic ulcer is the most common cause in

patients aged 3 to 5 years. (2) Mallory-Weiss tear is also a frequent cause in this age group and in older children. It is due to a mucosal laceration at the gastroesophageal junction usually secondary to excessive retching and vomiting. (3) In

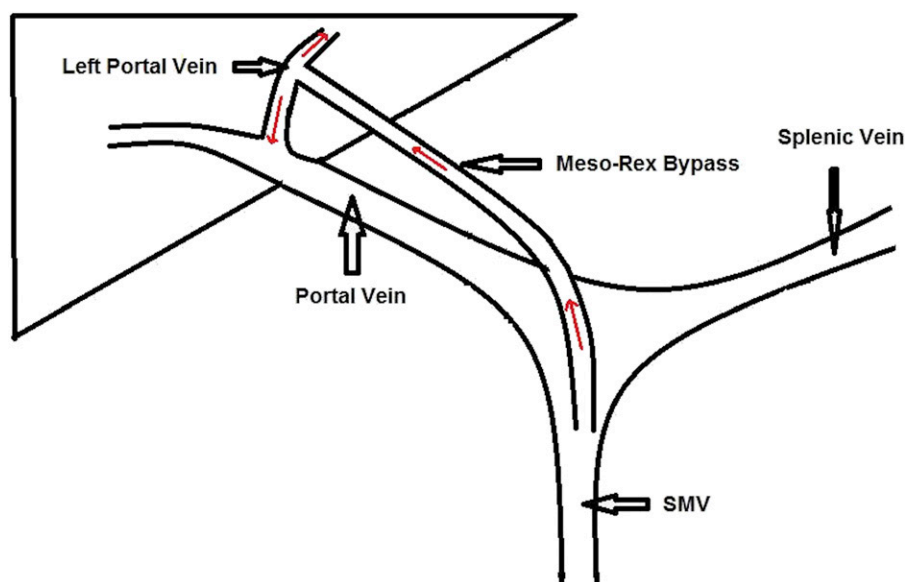


Figure 4. Meso-Rex bypass: graft bypassing the occlusion in the portal vein via conduit from the left portal vein to the superior mesenteric vein (SMV) with blood flow to the right portal vein.

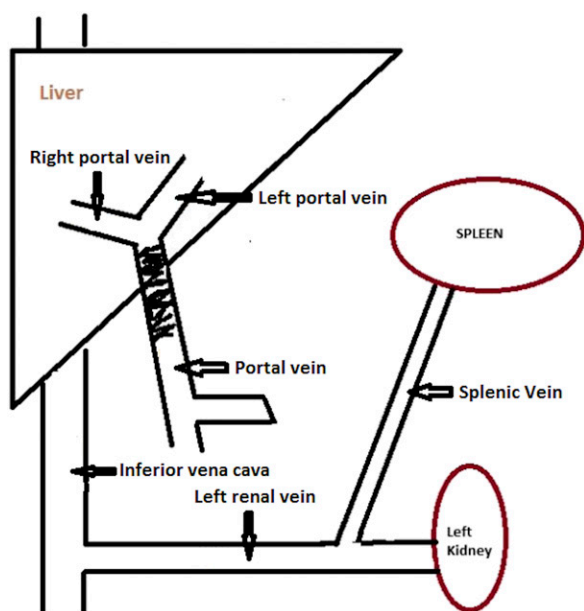


Figure 5. Distal splenorenal shunt: the splenic vein is surgically connected to the left renal vein.

children older than 5 years, esophageal varices secondary to portal hypertension is the most common cause and may present with life-threatening hematemesis. (2) The causes

of portal hypertension are multiple, 1 of which is extrahepatic portal vein obstruction (EHPVO).

EHPVO is defined as obstruction of the extrahepatic portion of the portal vein that may or may not involve the intrahepatic portal veins. (4) It, however, does not refer to isolated thrombosis of the splenic or superior mesenteric vein. (4) EHPVO is responsible for 5% to 10% of all cases of portal hypertension in developed countries and is most commonly secondary to underlying liver disease or malignancy (Table). (5)(6)

The portal vein is formed by the splenic vein and the superior and inferior mesenteric veins. It supplies 75% of the blood to the liver, and the remaining 25% is supplied by the hepatic artery. (7) In chronic EHPVO, the normal single-channel portal vein becomes bypassed by numerous tortuous collateral venous channels forming a portal cavernoma. It takes 3 to 5 weeks for these collateral venous channels to become fully established. (8)

Acute EHPVO may manifest with symptoms of abdominal pain and ascites but is often asymptomatic. As the portal cavernoma becomes unable to accommodate splenomesenteric inflow, signs of portal hypertension develop. (6)(9) Acute variceal bleeding is the most frequent and may be the first manifestation of a failing portal cavernoma. (9) The

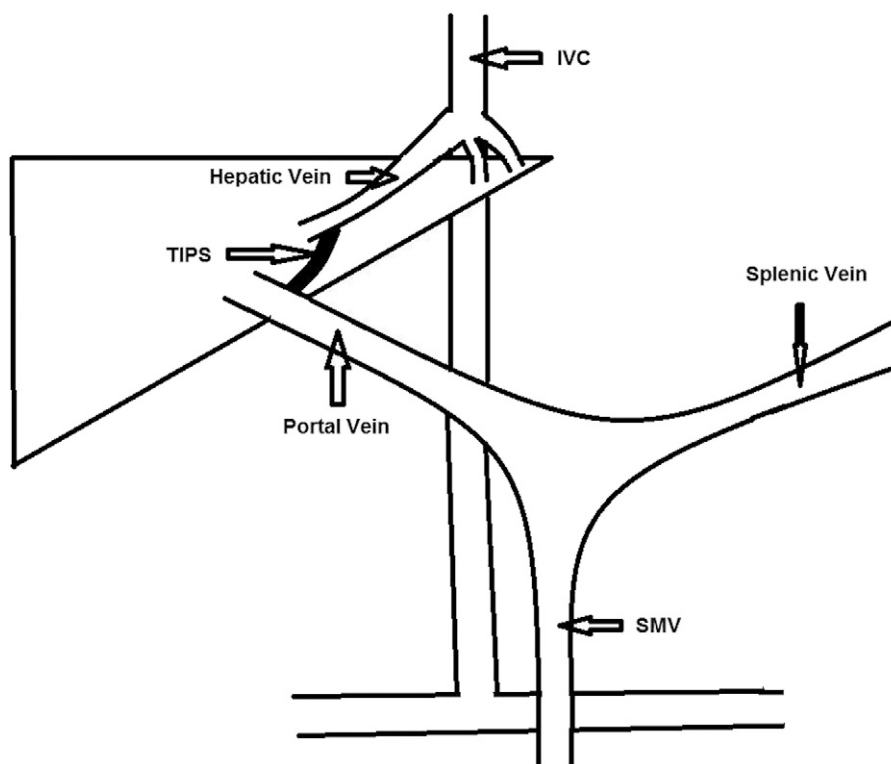


Figure 6. Transjugular intrahepatic portosystemic shunt (TIPS): the portal vein is connected to the hepatic vein. IVC=inferior vena cava, SMV=superior mesenteric vein.

gastroesophageal varices are usually large, and gastric varices are seen in 30% to 40% of patients. (10) Interestingly, ascites is a rare complication of chronic portal vein obstruction.

Our patient presented in hypovolemic hemorrhagic shock due to acute variceal bleeding. EGD demonstrated large gastric and esophageal varices, and CT confirmed the diagnosis of chronic EHPVO. Evaluation for a hypercoagulable condition revealed elevated anti- β_2 glycoprotein I antibodies, suggestive of APS. APS is an acquired autoimmune disorder that manifests as recurrent venous or arterial thrombi. (11) Diagnosis depends on characteristic clinical features and laboratory abnormalities on 2 or more samples collected at least 12 weeks apart.

DIAGNOSIS

Abdominal ultrasonography is a reliable, noninvasive technique to diagnose portal vein thrombosis and is the initial investigation of choice. (5) The overall sensitivity and specificity of Doppler ultrasonography in the diagnosis of portal vein thrombosis are reported to be 89% and 92%, respectively. (12) CT and magnetic resonance imaging provide additional information, such as thrombus extension (mesenteric veins are difficult to assess with ultrasonography), evidence of bowel infarction, and adjacent organ status. (13) EGD is necessary to demonstrate as well as manage bleeding esophageal/gastric varices, and a liver biopsy is necessary to rule out chronic liver disease, especially in a patient with abnormal liver function tests.

MANAGEMENT

The initial management of variceal bleeding is adequate resuscitation with fluid and blood products along with initiation of an intravenous proton pump inhibitor and octreotide drip. EGD is essential to demonstrate and manage the varices endoscopically. The most common endoscopic procedure used to control variceal bleeding is banding of the varices. Sometimes, placement of a

Sengstaken-Blakemore tube may be a last-ditch effort to tamponade bleeding if banding fails. Surgical methods are used to control variceal bleeding in children with EHPVO when it is unresponsive to medical/endoscopic therapy. These therapies may include a portosystemic shunt or the Rex bypass procedure. (14) The Rex bypass is a procedure in which portal flow is redirected into the liver and, therefore, is not a shunt procedure (Fig 4). (15) This is done by bringing mesenteric venous and splenic blood around the EHPVO into a patent intrahepatic portal venous system, most commonly the left portal vein. However, the Rex bypass is suitable only for patients with a patent intrahepatic portal vein branch, determined by portal venography in the operating room. The distal splenorenal shunt is the procedure of choice for those who are not candidates for the Rex procedure (Fig 5). Transjugular intrahepatic portosystemic shunt is feasible only in patients with a patent portal vein lumen (Fig 6).

Lessons for the Clinician

- Maintain a high index of suspicion for isolated esophageal/gastric varices in an adolescent with large-volume hematemesis even in the absence of other stigmata of portal hypertension (ascites, caput medusae, hemorrhoids).
- Although local epidemiology leads us to believe that *Helicobacter pylori* is a common cause of upper gastrointestinal bleeding in the pediatric population (incidence 3%–10% in developing countries and 0.5% in developed countries), variceal bleeding must remain high on the differential diagnosis and is the most common cause in children older than 5 years.
- Mallory-Weiss tear is a common cause of upper gastrointestinal bleed.
- Surgery is essential for patients who fail medical and endoscopic therapy.

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Case 4: Large-Volume Hematemesis in a 16-year-old Boy

Soham Dasgupta, Oluwabunmi O. Olaloye, Matthew A. Pierce and Andrea M. Glaser

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Index of Suspicion

4 Vomiting and Tachypnea in a 9-week-old Girl

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PRESENTATION

A previously healthy 9-week-old girl presents to the emergency department with vomiting and new onset of tachypnea. She was seen in the emergency department 3 days before this visit, monitored, and discharged with a diagnosis of viral gastroenteritis. Her symptoms continued, and she was again seen in the emergency department the next day. An abdominal radiograph revealed a nonobstructive bowel gas pattern. Abdominal ultrasonography was performed to assess for pyloric stenosis and was normal. She was discharged after she was able to drink an oral electrolyte solution without vomiting. She presents again with continued nonbloody, nonbilious vomiting, although her mother is also concerned because she is having abnormal breathing. A review of systems reveals poor feeding and decreased activity. A review of her growth chart shows an 800-g weight loss in 3 days. There are no sick contacts or recent travel. She was a term infant and has been healthy until now. Her parents are second cousins, but there is no family history of significant medical problems. She has recently received her 2-month vaccinations.

On physical examination she has a heart rate of 185 beats/min and a respiratory rate of 62 breaths/min. Her other vital signs are within age-appropriate limits. She had not been tachypneic on her previous visits. She appears fatigued, with a weak cry. She is tachypneic, with occasional grunting, but has good aeration and clear lung fields. Her cardiac examination findings are normal except for a capillary refill of 3 seconds. The remainder of her examination findings are within normal parameters. A diagnostic evaluation is commenced, and laboratory testing reveals the diagnosis.

DISCUSSION

Differential Diagnosis

The differential diagnosis for vomiting, tachypnea, tachycardia, and lethargy in infants should be broad. Infection should be among the first diagnoses considered in such patients. Gastroenteritis is the most common infectious cause of vomiting and dehydration leading to lethargy. Other gastrointestinal maladies, such as malrotation, volvulus, or even pyloric stenosis, should also be considered. Congestive heart failure should also be considered in patients with this presentation. Endocrine disorders, inborn errors of metabolism, and hydrocephalus or other neurologic pathology could also be considered.

AUTHOR DISCLOSURE Drs Otto, Orr, and Boyd have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

The Diagnosis

Laboratory evaluation included basic laboratory tests and a full sepsis evaluation, including blood, urine, and cerebrospinal fluid cultures. The complete blood cell count was normal. The basic metabolic panel showed a glucose level of 626 mg/dL (34.7 mmol/L), with a bicarbonate level less than 5 mEq/L (<5 mmol/L). The sodium level was 152 mEq/L (152 mmol/L), potassium level was 6.5 mEq/L (6.5 mmol/L), and chloride level was 123 mEq/L (123 mmol/L), with an anion gap greater than 24 mEq/L (>24 mmol/L). A whole blood ketone level was 3.6 mmol/L (normal, <0.6 mmol/L). A glycated hemoglobin level was performed and was 11.0%. Our patient was diagnosed as having diabetic ketoacidosis and was placed on a continuous insulin infusion.

The Condition

Neonatal diabetes mellitus (also known as congenital diabetes mellitus) is a rare disorder, occurring in approximately 1 of every 300,000 to 500,000 live births. In populations with significant consanguinity, neonatal diabetes mellitus has been reported in up to 1 in 21,000 births. Patients have impaired glucose sensing, leading to inappropriately low secretion of insulin in the setting of hyperglycemia. This is in contrast to type 1 diabetes mellitus, which is an autoimmune phenomenon wherein autoantibodies attack and destroy pancreatic β cells, leading to decreased production of insulin. Patients will present with a history of low birthweight, indicative of insulin's important role in utero in fetal growth. Persistent hyperglycemia causes excess diuresis, leading to failure to thrive and dehydration despite seemingly adequate intake. In addition to hyperglycemia and glucosuria, infants will often have biochemical features consistent with diabetes mellitus (ketonemia, ketonuria, elevated anion gap). A severe metabolic acidosis may lead to a compensatory hyperventilation, although the appearance of a tachypneic infant is often mistaken for respiratory infection despite absence of fever, cough, or wheezing. The time of presentation is variable, but the condition classically presents before 6 months of age, making autoimmune type 1 diabetes mellitus unlikely.

Neonatal diabetes mellitus is overwhelmingly a monogenic disorder, and molecular diagnostic testing is indicated for patients who present with clinical and biochemical evidence of diabetes mellitus before 6 months of age. The specific mutation can have a major effect on patients' clinical course and prognosis, with approximately 45% of patients with neonatal diabetes mellitus experiencing a transient course and 45% facing

permanent diabetes. Those with transient neonatal diabetes will have remission after a treatment period of several months to a year, although relapse later in life occurs frequently. Disturbances of imprinted genes at chromosome 6q24 represent approximately 70% of transient neonatal diabetes, with far fewer transient cases due to adenosine triphosphate-regulated potassium channel mutations (*ABCC8* and *KCNJ11*). Permanent neonatal diabetes mellitus is due to a host of gene mutations involved in glucose sensing and the subsequent secretion of insulin. The most common mutations are in *KCNJ11* and *ABCC8*, genes encoding for K_{ATP} channels that regulate insulin secretion after sensing glucose. Patients require lifelong glycemic monitoring and treatment for diabetes mellitus. Our patient was later found to be a compound heterozygote for 2 presumed pathogenic variants in the *ABCC8* gene.

Management

The first therapeutic step is to begin to restore extracellular fluid volume, which has been depleted through osmotic diuresis and vomiting. Children with diabetic ketoacidosis are at risk for cerebral edema if rehydration is too rapid. Initial fluid resuscitation should begin with no more than 10 to 20 mL/kg of an isotonic solution (such as saline or lactated Ringers solution) over the first 1 to 2 hours. Remaining fluid deficits should be calculated and replaced over the next 48 hours. Insulin must be given to allow normal carbohydrate metabolism and to stop ketogenesis. Serum hyperosmolality should be normalized gradually and potassium monitored closely and replenished as needed. After acidosis control is accomplished, patients are transitioned to subcutaneous insulin therapy. Some patients with *KCNJ11* or *ABCC8* mutations may achieve glycemic control with oral sulfonylurea monotherapy, eliminating the need for insulin injections; thus, obtaining a molecular diagnosis is key in neonatal diabetes mellitus because results inform the clinical course and family counseling. However, not all mutations will respond to sulfonylurea therapy. Our patient underwent a trial of sulfonylureas, but the trial was deemed unsuccessful due to poor glycemic control and she was transitioned back to subcutaneous insulin therapy.

Lessons for the Clinician

- Neonatal diabetes mellitus, although rare, should always be on the differential diagnosis for infants with vomiting, lethargy, tachycardia, and tachypnea with absence of typical respiratory infection findings, such as wheezing, cough, rhinorrhea, or fevers.

- A family history of consanguinity should raise suspicion for congenital disorders such as neonatal diabetes mellitus.
- Neonatal diabetes mellitus is characterized as transient or permanent, with approximately half of infants having a transient course resolving after weeks to months and half facing permanent diabetes mellitus.
- Although insulin is the first-line therapy in neonatal diabetes mellitus, infants should undergo a trial of oral

sulfonylureas to identify patients who may be able to wean off insulin therapy.

- Molecular diagnosis is key to identify the specific mutation to help inform therapy and prognosis, as well as guide family counseling.

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4 Weight Loss and Cough in a 12-year-old Boy

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AUTHOR DISCLOSURE Drs Holmberg, Owusu-Achaw, and Dwomo-Fokuo have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 12-year-old boy presents with 2 to 3 months of worsening cough and increasing fatigue. He is known to be retroviral positive and had been started on antiretroviral therapy 10 months earlier. At that time, he presented with fatigue and substantial weight loss of unclear amount, and it was discovered that his mother had recently died of AIDS. A rapid diagnostic test using an oral fluid sample was obtained and was positive for human immunodeficiency virus (HIV). He was started on antiretroviral therapy with zidovudine, lamivudine, and efavirenz, along with cotrimoxazole. He had weight gain and a decrease in symptoms after initiation of therapy, and, given his progress, his grandmother stopped his medications after 2 months of treatment.

On physical examination, he appears wasted and has a heart rate of 120 beats/min, a respiratory rate of 40 breaths/min, and a temperature of 98.4°F (36.9°C). He has thrush of the oropharynx and cervical lymphadenopathy. Auscultation of the lungs reveals diffuse crackles and coarse sounds. He has mild intercostal retractions, frequent cough, and the presence of digital clubbing. A chest radiograph was obtained and revealed bilateral perihilar adenopathy and innumerable widespread micronodular infiltrates throughout both lungs (Fig). A rapid test of a body fluid reveals the diagnosis.

DISCUSSION

Using morning gastric aspiration, a nucleic acid amplification test was positive for *Mycobacterium tuberculosis* and negative for rifampin resistance. Four-drug antituberculous therapy was initiated.

The Condition

Tuberculosis (TB) is an infectious disease caused by *M tuberculosis* and affects almost one-third of the population worldwide. In 2015, it is estimated that there were a total of 10.4 million new cases of TB. The following year, more than 25,000 children are estimated to have become newly infected. (1)(2) A disproportionate share of the disease burden is found in developing countries. These locations account for 95% of infections and 98% of mortality due to TB. (3) In children, limitations in diagnosing TB have resulted in significantly fewer

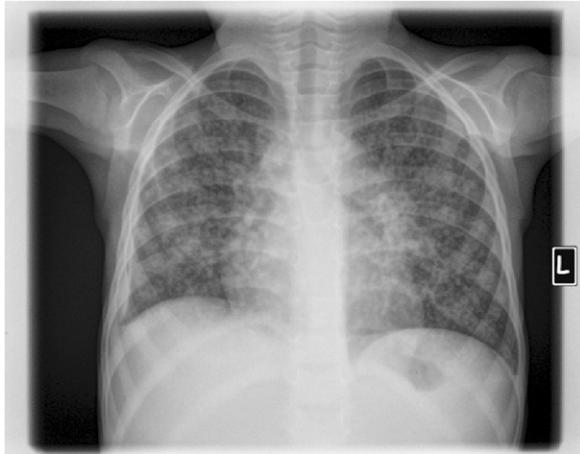


Figure. Chest radiograph revealing innumerable diffuse micronodules throughout both lungs along with bilateral perihilar adenopathy, left greater than right.

confirmed cases than actually occur. (2) This results in a lack of treatment for many children. The greatest risk of missed diagnosis is in children younger than 5 years, an age group that is responsible for half of all pediatric TB. (4) As a result, there is likely “a large and invisible burden of preventable child deaths related to tuberculosis.” (5)

Human immunodeficiency virus has had a profound effect on TB and continues to significantly alter the acquisition, transmission, and progression of tuberculous disease. (6)(7) This burden is especially pronounced in sub-Saharan Africa, where up to 80% of HIV/TB co-infections take place. In some African countries, 60% to 70% of new TB cases are in individuals with HIV. (3)(7)(8) The diagnosis of TB in HIV-infected individuals can be more difficult as skin testing and acid-fast bacilli smears are more likely to be falsely negative. Even in children with accurately diagnosed TB, those with HIV face a markedly higher mortality rate and an increased incidence of drug-resistant TB. (5)(6)

A systemic form of disease characterized by diffuse nodular tubercles has been labeled “miliary TB” due to the millet seed appearance of tubercles on roentgenography. Spread via the lymphohematogenous route, miliary TB can involve numerous organs and cause wide-ranging signs and symptoms related to the involved systems. Although rare in immunocompetent individuals, children with advanced HIV have a much higher likelihood of miliary disease. (9)

Differential Diagnosis

In TB-endemic areas, in children who present with chronic cough, weight loss, and possible exposure, a diagnosis of

TB should be strongly considered. In similar clinical presentations, other possibilities include *Pneumocystis jiroveci* pneumonia, atypical pneumonia, fungal infection, or an oncologic process. In addition, the chest radiographic findings could suggest Langerhans cell histiocytosis, viral pneumonia, hypersensitivity pneumonitis, pulmonary hemosiderosis or metastatic disease. CD4 counts can also be helpful when considering opportunistic infections. In general, the susceptibility to different infections correlates well with CD4⁺ levels. For example, *Candida* infection is more common when the CD4 count drops below 300 cells/mm³, whereas *Pneumocystis* and *Toxoplasma* infections are more likely after levels reach 200 cells/mm³ and 100 cells/mm³, respectively.

Diagnosis

The diagnosis of TB infection in children is difficult. Historically, sputum smears have been the standard method of identification. However, this is complicated by several factors. Children of young age are often unable to expectorate adequate sputum for sampling. Methods aimed at improving specimen collection include gastric aspiration and sputum induction. (10) Tuberculosis is often paucibacillary, and even adequate sputum samples may have too few bacilli present for diagnosis. (7) Skin testing and interferon- γ release assays are tests that use an individual’s natural immune response to *M tuberculosis* infection and are used in many areas of the world. Nucleic acid amplification testing (NAAT) is a relatively new technology in TB diagnosis and uses polymerase chain reaction. A specific cartridge-based NAAT has been recommended by the World Health Organization for use in children, a test that is also able to simultaneously test for rifampin resistance. Last, culture of *Mycobacterium* remains the gold standard of diagnosis but has significant limitations of its own. (11)

The diagnosis of miliary TB requires a high level of clinical suspicion. Signs and symptoms of miliary TB can be very nonspecific. Although fluid, tissue, and blood are extremely helpful in confirming systemic involvement, in settings where TB is endemic, clinical diagnosis is often the only method available. In these situations, the diagnosis of miliary TB can be made if a child has symptoms of TB, confirmed TB infection (based on the testing available), and classic miliary findings or diffuse reticulonodular lesions on imaging. (12)(13)

Treatment

First-line treatment for active, susceptible TB remains a 4-drug regimen using rifampin (RIF), isoniazid (INH),

pyrazinamide, and ethambutol for a defined interval, followed by INH and RIF for 18 additional weeks. In situations where children are unable to undergo routine eye testing, ethambutol is often foregone unless evidence of upper lobe disease is present. (14) Resistance to first-line antituberculous drugs has become a widespread problem. Tuberculosis that is resistant to INH and RIF is considered multidrug-resistant TB (MDR-TB), and additional resistance to an injectable agent and any fluoroquinolone is described as extensively drug-resistant TB. (15) According to the World Health Organization, there were almost 500,000 total new MDR-TB cases in 2015. (1) Treatment of MDR-TB generally uses sensitivity-based treatment with a fluoroquinolone as well as an injectable agent. (16) Extensively drug-resistant TB treatment involves more drugs (5–6 organism-susceptible agents) for a longer duration (≥24 months after negative cultures) than other regimens. (17) Children with any form of resistant TB who do not get appropriate treatment have a high likelihood of death. (2)(9)(13)

Outcome

The patient in our case eventually succumbed to disseminated TB infection and died despite appropriate therapy. This case reveals the importance of early diagnosis and adequate and consistent therapy, as well as the role that HIV co-infection plays in worldwide TB.

Lessons for the Clinician

- TB is a leading cause of mortality worldwide and is of particular importance in children affected by HIV.
- Drug-resistance to first- and second-line anti-TB agents is becoming a serious complicating factor in the treatment of individuals with TB infection.
- TB must be considered when caring for children with adequate exposure history and other risk factors such as HIV infection or other immune-suppression.
- TB commonly presents with hilar adenopathy on chest radiograph and the presence of diffuse micronodules is often specific to miliary TB.

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Case 4: Weight Loss and Cough in a 12-year-old Boy
Peter J. Holmberg, Eugene Owusu-Achaw and Adoma Dwomo-Fokuo
Pediatrics in Review 2019;40;46
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4 Acute Onset of Fever, Jaundice, and Hyponatremia in a 17-year-old Boy

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AUTHOR DISCLOSURE Drs Kovaric and Allen have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 17-year-old previously healthy boy presents with scleral icterus for 1 day. For approximately 10 days previously, he has had fever, arthralgias, and headache. He additionally complains of eye pain with movement, stiff neck, excessive thirst (drinking 64 oz of water a day), back pain, and nausea.

He denies rash, sore throat, cough, and congestion. He has not traveled anywhere. He has been taking approximately 8 g of acetaminophen daily for the past 2 weeks for joint pain.

On physical examination the patient's vital signs are normal except for fever (to 101.7°F [38.7°C]). He has scleral icterus, no periorbital swelling or edema, no meningismus, no hepatomegaly or splenomegaly, no swelling of the joints, and insect bites on his ankles but no rash.

Laboratory evaluation reveals the following values: sodium, 126 mEq/L (126 mmol/L); white blood cell count, 14,600/ μ L (14.6×10^9 /L), with 75.5% neutrophils and 22% lymphocytes; hemoglobin, 12.6 g/dL (126 g/L); platelet count, $79,000 \times 10^3$ / μ L ($79,000 \times 10^9$ /L); acetaminophen level, less than 2 μ g/mL ($<13.23 \mu$ mol/L); total bilirubin, 8.9 mg/dL (152.2 μ mol/L); direct bilirubin, 5.8 mg/dL (99.2 μ mol/L); lipase, 1,278 U/L (21.3 μ kat/L); aspartate aminotransferase, 252 U/L (4.2 μ kat/L); alanine aminotransferase, 241 U/L (4.0 μ kat/L); alkaline phosphatase, 267 U/L (4.5 μ kat/L); albumin, 2.7 g/dL (27 g/L); prothrombin time, 13.5 s; partial thromboplastin time, 33.9 s; blood urea nitrogen, 14 mg/dL (5 mmol/L); and creatinine, 1.0 mg/dL (88.4 μ mol/L). Urine specific gravity is 1.006.

Poison control is consulted for chronic supratherapeutic acetaminophen ingestion and recommends acetylcysteine therapy. Liver enzyme levels decrease only slightly on acetylcysteine, and a fourth bag of acetylcysteine is started.

Additional history and laboratory examination reveal the diagnosis.

DISCUSSION

The adolescent's persistent fevers and the lack of improvement in his transaminase levels despite treatment with acetylcysteine prompted an infectious disease consultation. On further history, the patient revealed that the insect bites

on his ankles were flea bites. Rodents had been seen in the home. In addition, the patient had cats and a dog that slept in his bed.

The patient was started on doxycycline, with resolution of symptoms within a day. A week later, his rickettsial panel returned with a typhus IgM titer of 1:1,024 and a typhus IgG titer of 1:1,024.

The Condition

Endemic or murine typhus usually presents with a triad of fever, headache, and rash. The rash is a nonpruritic macular or maculopapular rash starting on the trunk and spreading peripherally, sparing the palms and soles. However, in half the cases, rash is not present. (1)(2) Other clinical manifestations include arthralgias, pain with eye movement, cough, abdominal pain, confusion, and stiff neck. In 10% of patients, organ-specific complications arise (pneumonitis, hepatitis, meningoencephalitis, and renal failure); 2% to 4% of cases are considered severe, with shock, respiratory distress, multiple organ failure, hemorrhagic diathesis, consumptive coagulopathy, and severe neurologic compromise. (3)

Endemic typhus is caused by *Rickettsia typhi*, a gram-negative intracellular bacteria. Fleas spread *R typhi* from reservoirs (typically rodents) to humans via flea feces. Most commonly, flea feces are inoculated into the flea bite site, but flea feces can also be inhaled.

Endemic typhus should be distinguished from epidemic typhus. Epidemic typhus is spread by the human body louse and is caused by *Rickettsia prowazekii*. Epidemic typhus is more common in conditions of overcrowding and poor hygiene, such as in prisons and refugee camps.

Worldwide, endemic typhus is usually found in temperate climates and coastal areas in Asia, Australia, Mexico, and Spain. In the United States, endemic typhus can be found in southern Texas and California. This patient resided in central Texas, where there has been an increase in typhus cases since 2008. In 2008, after 13 cases of murine typhus were reported within 5 months, an investigation was conducted. The investigators found evidence of emergence of a suburban life cycle of endemic typhus involving cats, dogs, raccoons, and opossums and their fleas (in contrast to the urban life cycle, which is composed of rats and fleas). (4)

Diagnosis

The gold standard for diagnosis is indirect immunofluorescent antibody assay. (3) However, treatment should not be delayed while awaiting results. Additional laboratory abnormalities may include elevated aminotransferase levels, leukopenia, and thrombocytopenia. Some patients may have evidence of pneumonitis on chest radiography. Hyponatremia

is most commonly attributed to increased vascular permeability due to endothelial cell injury by *Rickettsia typhi*, resulting in low intravascular volume and concentrated urine. Interestingly, our patient continued to have excessive thirst after admission, drinking 2,500 mL over 24 hours on the inpatient unit (even while receiving maintenance intravenous fluids with normal saline) and had dilute urine (urine specific gravity of 1.006) without evidence of renal injury (blood urea nitrogen level, 14 mg/dL [5 mmol/L]; creatinine level, 1.0 mg/dL [88.4 μ mol/L]). He was persistently hyponatremic until we changed his diet to nil per os and continued his maintenance fluids with normal saline. To our knowledge, there is no pathophysiologic explanation of our patient's excessive thirst.

Of note, when considering rickettsial disease, a rickettsial panel is preferred because there is cross-reactivity between Rocky Mountain spotted fever (RMSF) and *R typhi* antibodies. (Both IgG and IgM are cross-reactive, but, per the Centers for Disease Control and Prevention [CDC], IgG antibodies are more accurate than IgM.)

In our patient's case, acute titers, taken 2 weeks after onset of symptoms, showed a typhus IgG titer of 1:1,024 as well as an RMSF IgG titer of 1:64. Convalescent titers showed typhus IgG 1:512 and RMSF IgG 1:256. Acute and convalescent titers were performed at 2 different laboratories so that a direct comparison between acute and convalescent titer numbers is difficult. The Texas Department of Health and Human Services classified this case as "probable typhus" because typhus IgG titers were higher than RMSF and the typhus IgG titer was 1:1,024 in the typhus-endemic area of Travis County. (2)(5)

Treatment

Doxycycline is the antibiotic of choice and has been shown to shorten the duration of illness. According to the *Red Book*, doxycycline should be given regardless of age. (6) Rapid resolution of symptoms, as in our patient, helps to confirm the diagnosis before serologic results are available.

Prevention

Prevention measures include treating domestic dogs and cats for fleas, preventing exposures to stray animals, placing screens on the windows, and eliminating food sources for animals by securing trash cans and pet food and throwing away fallen food. (7)

Lessons for the Clinician

- Although typhus is characterized by a triad of fever, rash, and headache, rash is absent in half of the patients.
- Consider rickettsial diseases in the differential diagnosis of patients with fever, arthralgias, headache, rash,

hyponatremia, thrombocytopenia, leukopenia, and organ dysfunction or inflammation.

- Begin therapy in suspicious cases immediately; do not await serologic results.
- Typhus can be found in suburban areas of Texas and California, with common reservoirs being cats, dogs, raccoons, and opossums.

- Send a rickettsial panel because there is cross-reactivity between Rocky Mountain spotted fever and *Rickettsia typhi* antibodies.

References for this article are at <http://pedsinreview.aappublications.org/content/40/3/148>.

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4 An Infant with Status Epilepticus and Stroke

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PRESENTATION

A 33-day-old boy is admitted to the hospital with seizure episodes. The antenatal course was complicated by gestational diabetes mellitus and group B streptococcus (GBS) urinary tract infection for which the mother received intrapartum antibiotic drug therapy. The patient was born at term by induced vaginal delivery because of prolonged rupture of membrane but with Apgar scores of 8, 9, and 9 at 1, 5, and 10 minutes, respectively, without any birth asphyxia, meconium aspiration, and nuchal cord. On the day of admission, the patient started having tonic-clonic movement involving the left upper extremity associated with left arm extension, fisting of the left hand with squeezing movement, and eye deviation to the left associated with grunting. He continues to have seizures until he is given 4 doses of intravenous lorazepam 0.1 mg/kg, a loading dose of levetiracetam 20 mg/kg intravenously, and phenobarbital 20 mg/kg intravenously. He also presents with fever (rectal temperature of 102.9°F [39.4°C]), which is treated with 10 mg/kg of rectal acetaminophen twice.

On examination, peripheral capillary refill is 3 seconds. He has no spontaneous eye opening but is responding to painful stimuli. The anterior fontanelle is bulging, and pupils are 2 mm and reacting normally. Funduscopic examination did not show retinal hemorrhage, but optic disc margins were not clear bilaterally. Movement is diminished overall, but no movement of the left upper and lower extremities is present. The Moro reflex is incomplete, but rooting and sucking reflexes are present. Four beats of ankle clonus are present bilaterally. Initial laboratory evaluation demonstrates a C-reactive protein level of 1.57 mg/L (14.9 nmol/L) (reference range, <9.10 mg/L [<86.7 nmol/L]), a calcium level of 8.4 mg/dL (2.1 mmol/L), capillary blood pH 7.35 with P_{CO_2} of 38 mm Hg, and a lactate level of 18 mg/dL (2 mmol/L). A complete blood cell count reveals a total white blood cell count of $2,100/\mu\text{L}$ ($2.1 \times 10^9/\text{L}$), with 33% lymphocytes and 49% neutrophils, and Gram-positive cocci are found in the blood.

AUTHOR DISCLOSURE Drs Abdul Kather and Set have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. Dr Set's current affiliation is Division of Pediatric Neurology, Dayton Children's Hospital, Dayton, OH.

DISCUSSION

The cerebrospinal fluid (CSF) findings showed a red blood cell count of $24/\mu\text{L}$ ($0.000024 \times 10^{12}/\text{L}$), a white blood cell count of $66/\mu\text{L}$ ($0.066 \times 10^9/\text{L}$) (neutrophils 93%, monocytes 1%), a glucose level of 17 mg/dL (0.94 mmol/L), a protein level of 0.22 g/dL (2.2 g/L), and gram-positive cocci, suggestive of bacterial meningitis.

Clinical Course and Management

The patient was started on broad spectrum antibiotic drug therapy because there were concerns for meningitis. Head ultrasonography showed bilateral subdural effusions consistent with bacterial meningitis. An electroencephalogram showed diffuse neuronal dysfunction and focal seizures from the right central parietal region.

Magnetic resonance imaging (MRI) performed on day 2 showed a right posterior frontal anterior parietal acute infarct involving the precentral and postcentral gyrus (Fig 1). Also, there was multifocal loculated diffusion restriction, likely a collection of pus or small subdural empyema around the frontal and parietal convexity more on the right side, fitting the clinical presentation (Fig 2). Contrast-enhanced MRI of the brain showed leptomeningeal enhancement consistent with meningitis (Fig 3). There were no visible retinal hemorrhages found in gradient echo MRI; therefore, suspicion of child abuse was low, but it was included in the differential diagnosis initially. Also, a dilated eye examination did not show retinal hemorrhage.

The patient had a prolonged episode of seizure progressing to status epilepticus. He was started on a midazolam

drip (continued for 5 days) with an increased dose of levetiracetam (60 mg/kg per day) and phenobarbital (5 mg/kg per day). The culture returned positive for *Streptococcus agalactiae* sensitive to ampicillin. A central venous catheter was placed, and ampicillin therapy was continued. Clinically, the patient stopped having seizures, and the weakness of the left upper extremity improved. MRI, electroencephalography, and lumbar puncture were repeated on day 29 (Figs 1–3).

On day 29, MRI showed cystic encephalomalacic changes in the right parietal lobe with the resolution of extra-axial diffusion restriction and substantial improvement of leptomeningeal enhancement (Fig 3). CSF continued to show 26 nucleated cells, 59% neutrophils. CSF culture showed no growth. After 33 days of ampicillin therapy, the central line was removed and the patient was discharged on oral levetiracetam and phenobarbital.

Final Diagnosis

The infant was diagnosed as having severe late-onset bacterial GBS meningitis with acute stroke, subdural empyema, and status epilepticus.

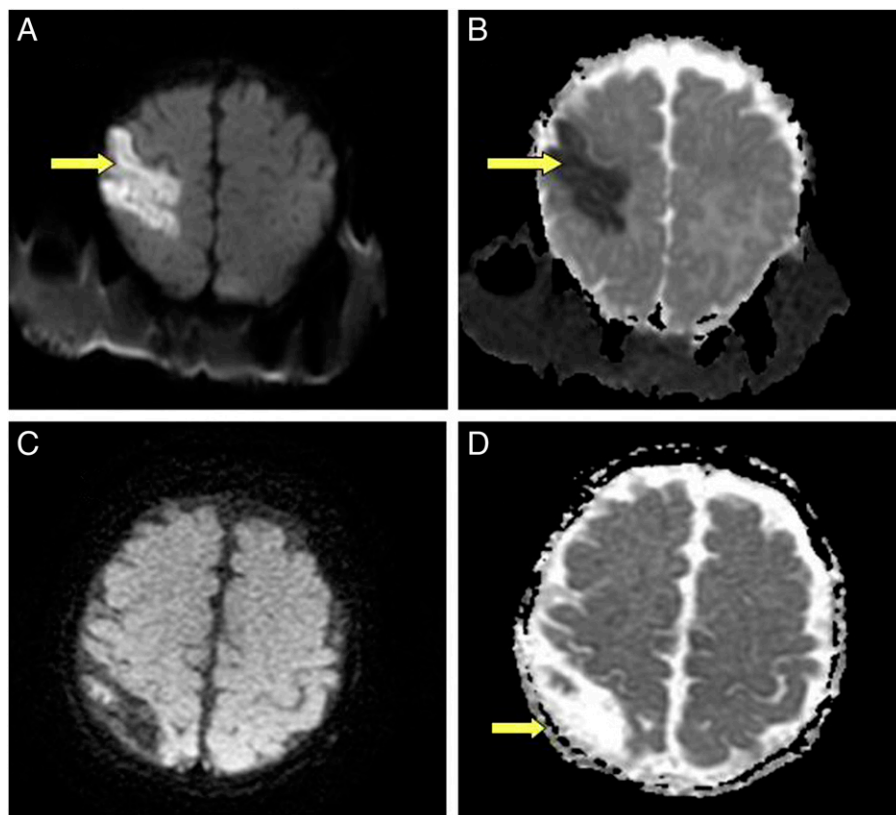


Figure 1. Magnetic resonance imaging of the brain. A and B. Diffusion-weighted image and apparent diffusion coefficient image demonstrate a focal, parenchymal, somewhat wedge-shaped diffusion restriction (yellow arrows) along the right precentral and postcentral gyrus. C and D. There is no diffusion restriction after treatment, but encephalomalacic changes (yellow arrow) are noted.

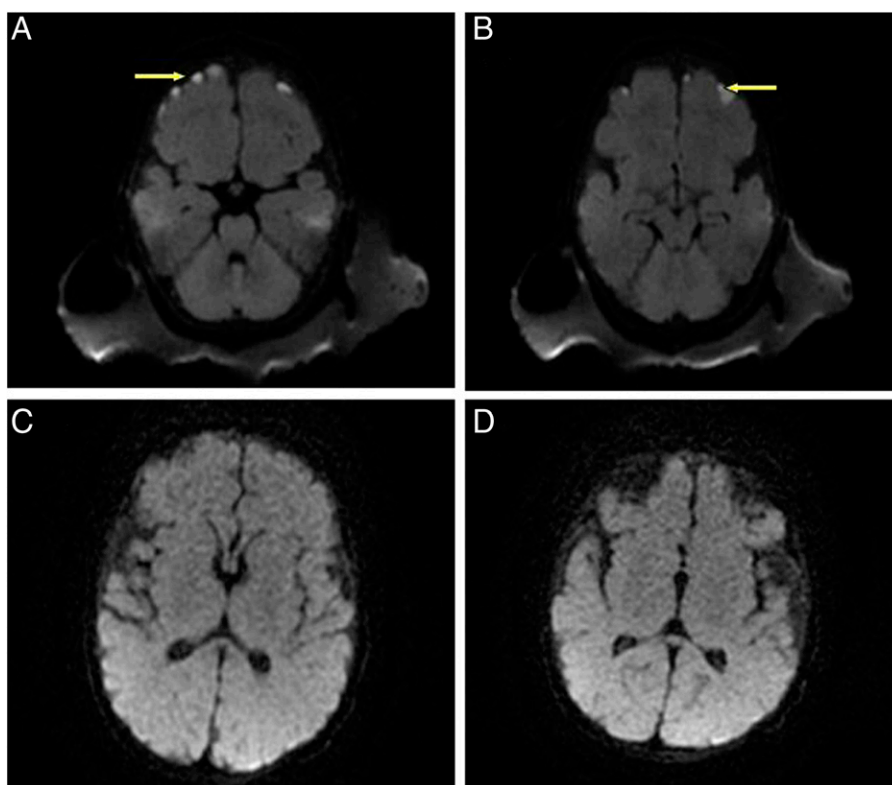


Figure 2. Magnetic resonance imaging of the brain. A and B. Multifocal small diffusion restriction (yellow arrows) along the frontal and parietal convexity is more prompt on the right side, raising the possibility of subdural empyema. C and D. The restriction disappeared after treatment.

The Condition

Bacterial meningitis is a pia-arachnoid infection and an inflammatory response in the CSF. It is a common manifestation of late-onset (day 7–89 after birth) neonatal sepsis. It occurs in 25% of neonates with bacteremia, with an incidence ranging from 0.25 to 1 per 1,000 live births. In developed countries, bacterial meningitis is commonly caused by GBS serotype III, accounting for 50% to 78%

of all cases. Late-onset infections suggest nosocomial or community acquisition, or perinatal transmission from human milk, although the maternal flora colonizing the neonate may still be a source of infection.

Universal screening of pregnant women in the United States for rectovaginal GBS colonization at 35 to 37 weeks' gestation and administration of intrapartum antimicrobial prophylaxis to carriers has reduced the incidence of early-onset

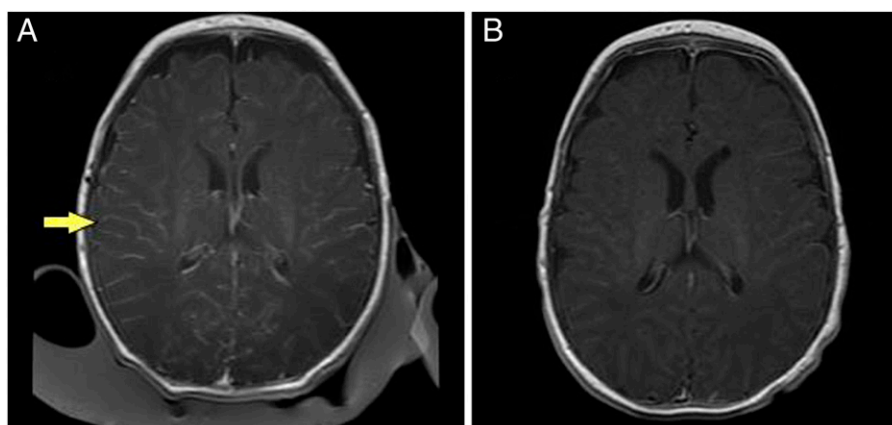


Figure 3. Magnetic resonance imaging of the brain. A. Leptomeningeal enhancement (yellow arrow) is seen after gadolinium administration. B. Enhancement disappears after treatment.

disease, but the incidence of late-onset disease has remained stable at an average of 0.34 per 1,000 live births in the United States.

GBS infection presents with symptoms such as fever (81%), irritability/crying (42%), and poor feeding (39%). Twenty percent to 50% of infants with meningitis present with seizures. Up to 50% of infants with a history of meningitis will be neurologically impaired, and 25% will have a severe disability. Meningitis is a very rare cause (~3%) of arterial ischemic stroke in children. Hernández et al showed that the penetrating lenticulostriate and thalamostriate arteries, which supply the basal ganglia, thalamus, and deep white matter, are mostly affected (88%), and superficial cortical infarction was observed in 75% of patients.

Common neurologic complications of meningitis include ventriculitis (20%), cerebral edema and increased intracranial pressure (78%), seizures (17%–40%), cerebral infarction (30%–50%), subdural effusion or empyema (7%–33%), hydrocephalus (24%), hearing loss (7%–12%), intellectual disability (4%), and developmental delay (25%). The uncommon neurologic complications of meningitis are spinal cord ischemia, brain abscesses, aneurysm formation of focal intracranial vessels, and cortical visual loss.

Eight percent to 33% of infants with bacterial meningitis have accumulation of extra-axial fluid or subdural collection of pus. This may, in turn, become an empyema, which is present in up to 1% of affected patients. If not treated early and properly, this may require surgical drainage.

Empirical therapy of possible neonatal meningitis should include intravenous ampicillin (300 mg/kg per day) or cefotaxime plus gentamicin (4–5 mg/kg per day). Once

GBS have been identified and the susceptibility verified, penicillin G (450,000–500,000 U/kg per day) can be used to complete therapy for a minimum of 14 days and should be extended to 21 days or longer if complicated. Seizures are controlled with first-line antiepileptic drugs such as lorazepam, diazepam, phenobarbital, phenytoin (older babies), and levetiracetam for 1 week up to 12 months after the last seizure, and patients should regularly follow up with a neurologist.

Lessons for the Clinician

- Despite recent advances in neonatal intensive care, rapid diagnosis, and treatment, neonatal bacterial meningitis is one of the most common causes of neurologic disability.
- Despite prophylactic intrapartum antibiotic drug therapy, late-onset group B streptococcus infections in infants continue to occur and are associated with higher morbidity than are early-onset infections.
- High clinical suspicion, early diagnosis, immediate institution of therapy, and early recognition and management of complications can decrease the mortality rate and result in a better neurologic outcome.
- Subdural effusions could have been from shaking, and the stress of abuse can lead to group B streptococcus infection. Severe shaking can also cause a brain infarct and fever. So, a dilated retinal examination, magnetic resonance imaging of the eye with gradient-recalled echo sequence, or a skeletal survey is needed to exclude child abuse/inflicted brain injury.

Suggested Readings for this article are at <http://pedsinreview.aappublications.org/content/40/8/431>.

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4 Delayed Passage of Meconium, Abdominal Distention, and Emesis in a 2-day-old Girl

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PRESENTATION

A full-term newborn is delivered via normal spontaneous vaginal delivery to a 38-year-old gravida 5, now para 5005 mother. The mother underwent elective induction of labor for preeclampsia without severe features. The mother received adequate prenatal care, and serologic tests were negative apart from group B *Streptococcus* colonization, for which she received adequate intrapartum antibiotic prophylaxis. The labor and delivery course was uneventful, and Apgar scores were 9 and 9 at 1 and 5 minutes, respectively, with suction, drying, and stimulation. Birthweight was 3,270 g (appropriate for gestational age); length, 52 cm; and head circumference, 33 cm. For the first 24 hours after delivery, the infant took the bottle well, with minimal regurgitation. The abdomen was soft and nondistended. Now, on postnatal day 2, her intake by mouth is decreased, her abdomen has become firm and distended, and she is having more large-volume emesis that is nonbloody and nonbilious. She has also failed to pass meconium for more than 24 hours. Abdominal radiographs are obtained that show multiple dilated loops of bowel with absence of distal air, consistent with a distal bowel obstruction (Fig 1). An urgent surgical consult is requested and a nasogastric tube is placed, the output of which becomes frankly bilious over the next few hours. Of note, the infant has a half-sister with a history of Hirschsprung disease requiring diverting loop ileostomy.

DISCUSSION

Differential Diagnosis of Delayed Passage of Meconium

This differential diagnosis includes colonic aganglionosis (Hirschsprung disease), intestinal atresia/webs, malrotation with or without volvulus, anorectal malformations, meconium ileus (usually secondary to cystic fibrosis), meconium plug syndrome, small left colon, drugs during delivery (magnesium sulfate, opiates, or ganglionic blocking agents), or hypothyroidism. Another cause could be functional ileus, which occurs in the setting of prematurity, sepsis, respiratory distress, pneumonia, or electrolyte disturbances.

Delayed passage of meconium itself, without other concerning symptoms, does not necessarily warrant urgent surgical consultation. However, particularly in light of the bilious output that emerged after nasogastric tube placement in this case, some of the more serious anatomical malformations included in our differential diagnosis should be considered. These do require immediate

AUTHOR DISCLOSURE Drs Mataya and Lysouvakon have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Abdominal radiograph showing distended, tubular-like bowel loops with absence of distal air.

surgical consultation and intervention to avoid gut perforation or compromised gut viability. The urgent or “stat” timing of this consultation is particularly important if abdominal radiographs are abnormal (ie, show a pattern



Figure 2. Contrast enema radiograph showing total microcolon on a background of distended small-bowel loops.

of intestinal obstruction or perforation). In fact, some pediatric surgeons have argued that any term baby with bilious vomiting should undergo an upper gastrointestinal contrast study to definitively exclude malrotation, given the serious nature of this problem and its potentially devastating sequelae.

Given this infant’s family history of Hirschsprung disease, delayed passage of meconium for more than 24 hours, as well as the abdominal radiographs concerning for distal bowel obstruction, a lower gastrointestinal contrast study was obtained. This showed total microcolon on a background of distended small-bowel loops concerning for distal small-bowel atresia or total colonic aganglionosis, also known as Hirschsprung disease (Fig 2). This narrowed the differential diagnosis significantly, and she was taken to the operating room late on postnatal day 2 for definitive diagnosis of total colonic with small-bowel aganglionosis (involvement up to 80 cm proximal to the ileocecal valve).

The Condition

Hirschsprung disease consists of a collection of conditions that have aganglionosis of the intermyenteric plexus as a common feature. It is classified into ultra-short-, short-, and long segment disease. Long-segment disease is further classified into colonic, total colonic, and total colonic with small-bowel aganglionosis. Total colonic aganglionosis is an uncommon form of Hirschsprung disease, affecting 2% to 13% of Hirschsprung cases. Affected families can carry a 200 times higher risk of recurrence. The initial presentation of long-segment disease is often functional obstruction at or shortly after birth, although a later presentation is not uncommon. Radiologic diagnosis, particularly in newborns, is difficult because findings are not consistent. However, there are distinct patterns seen with contrast enema that are being identified with an increased likelihood of total colonic aganglionosis: microcolon and question mark-shaped colon. Hirschsprung disease is generally thought to be a genetic, sex-modified, multifactorial condition with variable severity and incomplete penetrance. Total colonic aganglionosis, however, may have a different signaling pathway because it is much more common in familial series, and length of involvement increases with successive generations (suggesting a possible autosomal dominant inheritance pattern with increased gene penetrance in successive generations). The *RET* and *EDNRB* genes are the 2 major susceptibility pathways for Hirschsprung disease and total colonic aganglionosis.

Complications, Treatment, and Outcomes

Either before surgery or in the immediate postoperative period, Hirschsprung-associated enterocolitis is a major life-threatening complication that can affect up to half of these patients. This can present as abdominal distention, explosive diarrhea, emesis, fever, lethargy, and even shock. Surgical management of total colonic aganglionosis via a variety of techniques has been shown to be successful. However, results are suboptimal, sequelae are very common, and mortality is relatively high (~15%), particularly in those with extensive small-bowel involvement. Patients with this condition often undergo multiple complications and reoperations. In general, patients start with a stoma and are eventually reconnected to allow voluntary bowel movements. Approximately half of the patients achieve good bowel control long term, and the other half have problems maintaining continence. They will start with an average of 5.2 bowel movements per day, decreasing to 3.4 at age 15 years. Iron deficiency anemia and growth delay are also common sequelae in these patients.

Lessons for the Clinician

- Most full-term neonates will pass meconium in the first 24 hours of postnatal life. Failure to pass meconium after 48 hours, or sooner if other concerning symptoms are present, would warrant an investigation as to the cause of the delayed passage of meconium.
- Urgent or “stat” surgical consultation is of the utmost importance in cases of delayed passage of meconium that are accompanied by other concerning symptoms, such as bilious emesis or a firm and distended abdomen.
- Hirschsprung disease, including total colonic aganglionosis, is a rare yet clinically significant cause of delayed passage of meconium, abdominal distention, and feeding intolerance in the neonatal period.

Suggested Readings for this article are at <http://pedsinreview.aappublications.org/content/40/6/310>.

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Leslie Mataya and Poj Lysouvakon

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4 Thrombocytopenia and Hematochezia in an Infant

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PRESENTATION

A 6-week-old white boy presented to his primary care provider with complaints of bloody stools and petechiae and was found to be thrombocytopenic, with an initial platelet count of $25 \times 10^3/\mu\text{L}$ ($25 \times 10^9/\text{L}$). The complete blood cell (CBC) count was otherwise normal. The mother's platelet phenotype was PLAI positive, ruling out neonatal allo-immune thrombocytopenia. The infant's primary care provider recommended a milk and soy protein-free diet for the mother (the infant was exclusively breastfed), reasoning that the hematochezia and thrombocytopenia may have been unrelated. After this maternal dietary intervention, the infant's symptoms abated transiently.

Hematochezia, petechiae, and thrombocytopenia recurred at age 4 months, at which time the platelet count was $19 \times 10^3/\mu\text{L}$ ($19 \times 10^9/\text{L}$), prompting further evaluation. Medical history revealed spontaneous vaginal delivery at 39 weeks' gestation, mild eczema, and intermittent nasal congestion. The family history was significant for immune thrombocytopenia in his paternal grandfather in later adulthood but was otherwise noncontributory. Physical examination revealed height, weight, and head circumference to be normal. There was no evidence of dysmorphism. The patient was afebrile, with normal vital signs. Examination was remarkable for pinpoint petechiae involving the face, trunk, and lower extremities. There was no organomegaly or lymphadenopathy. The remainder of the examination findings were normal.

Evaluation included prothrombin time/partial thromboplastin time, fibrinogen, and ultrasonography of the abdomen, all of which were normal.

On review of the peripheral blood film, platelets were noted to be uniformly small. The mean platelet volume (MPV) determined on the CBC count was low at 7.3 fl (reference range, 8.5–12 fl) (Fig). Bone marrow evaluation revealed adequate numbers of megakaryocytes with normal morphology and was otherwise normal.

Because microthrombocytopenia can be associated with abnormalities in immunoglobulin (Ig) levels, these were measured and revealed an elevated serum IgA level of 141 mg/dL (reference range, 27–66 mg/dL); IgM was in the lower range of normal at 42 mg/dL (reference range, 40–143 mg/dL), and IgG was within normal limits.

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Figure. Peripheral blood smear from the patient. The arrow points to microthrombocyte.

The patient received 2 U of platelets, with an increase in platelet count to $143 \times 10^3/\mu\text{L}$ ($143 \times 10^9/\text{L}$) but with a gradual decrease to $29 \times 10^3/\mu\text{L}$ ($29 \times 10^9/\text{L}$) over 9 days. He remained platelet transfusion dependent, requiring transfusions for severe thrombocytopenia associated with hematochezia. By 5 months of age, refractoriness to platelet transfusions developed, which was unimproved with intravenous immunoglobulin but responded to oral corticosteroids, suggesting development of an autoimmune component.

Abnormalities of the peripheral blood morphology and MPV led to further testing, which proved diagnostic.

DISCUSSION

The finding of microthrombocytopenia prompted genetic evaluation for Wiskott-Aldrich syndrome (WAS), an X-linked disorder. A splice site mutation at Xp c.559+5 G>C (guanine to cytosine) was detected. A splice site is the location in a gene where processing of precursor RNA into mRNA takes place. (1) A mutation at this position generally has a profoundly negative effect on the synthesis and function of the protein produced. This mutation was confirmed, and expression of the WAS protein was measured in the patient's platelets and in donor lymphocytes, revealing a decreased ratio of 0.17 (reference range, 0.71–1.31). Genotyping of the mother was also completed, confirming carrier status.

The Condition

The WAS gene consists of 12 exons and 1,823 base pairs on the X chromosome, encoding 502 amino acids. (2) Expression

is limited to hematopoietic cells. This protein is known to be involved in T-cell signaling and actin filament structure, contributing to megakaryocyte differentiation and formation of the immune synapse. (3) There is a large spectrum of phenotypes associated with mutations of the WAS gene ranging from isolated thrombocytopenia to the classic triad of thrombocytopenia, eczema, and immunodeficiency. Correlation of specific mutations and phenotypes has been reported, but many mutations have not been well characterized.

Management

The patient underwent stem cell transplant with a 10/10 human leukocyte antigen (HLA)-matched unrelated donor. Pretransplant conditioning consisted of busulfan, cyclophosphamide, and alemtuzumab. Tacrolimus and methotrexate were administered prophylactically to prevent graft-versus-host disease. The posttransplant course was complicated by the development of veno-occlusive disease, rotavirus infection, and *Clostridium difficile* colitis. Marrow engraftment was achieved 30 days after transplant, and the patient is now more than 400 days posttransplant with no evidence of WAS.

This case identifies a previously unreported mutation of the WAS gene with a severe phenotype requiring stem cell transplant. Previously, an individual had been reported with an alternate base pair substitution at the same locus who demonstrated a much milder phenotype.

Lessons for the Clinician

- The value of the peripheral smear review is illustrated by this case. Because mean platelet volume (MPV) is measured in the laboratory but not reported on the electronic medical record, the finding on the peripheral smear of small platelets was pivotal in the decision to review the MPV and to test for Wiskott-Aldrich syndrome (WAS), leading to early diagnosis, which likely contributed to successful transplant.
- Although rare, WAS should be considered in a male infant with unexplained thrombocytopenia; genetic testing is available commercially.
- Early diagnosis is valuable in WAS because these patients are susceptible to severe bleeding and infection. Also, allosensitization via multiple transfusions makes stem cell transplant more difficult.

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4 Altered Mental Status in a 6-year-old Boy

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AUTHOR DISCLOSURE Drs Thusang, Onyearugbulem, Chao, and Skaricic have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy 6-year-old boy presents to the emergency department with a 5-day history of fever, sore throat, and worsening cough. One day before presentation he was found to be difficult to arouse. On the day of hospital admission he is restless and minimally responsive to his mother's commands.

On physical examination his vital signs are normal. He is minimally responsive, does not follow commands, and opens his eyes to noxious stimuli. His neck is supple, with no neck stiffness, and his pupils are 3 mm, symmetrical, and reactive to light. He is uncooperative for a fundoscopic examination, and extraocular muscle movements are full and intact, without nystagmus. There is no facial asymmetry, his tongue is midline, and his palate elevates symmetrically with a strong gag response. His power is greater than 3/5 in all muscle groups, with normal tone and bulk. Deep tendon reflexes are 2+ throughout. Toes are down going to plantar stimulation bilaterally.

A blood glucose level, a complete blood cell count, and results of a basic metabolic panel are normal. A routine urine toxicology screen is negative, and acetaminophen and salicylate levels are undetectable. Computed tomography without contrast of the brain shows no acute intracranial hemorrhage, mass effect, or midline shift. Cerebrospinal fluid (CSF) is clear, with a red blood cell count of 19 per μL ($0.018 \times 10^9/\text{L}$) and a white blood cell count of $40/\mu\text{L}$ ($0.04 \times 10^9/\text{L}$) with lymphocytic predominance (90%). His CSF protein level is 0.02 g/dL (0.20 g/L) and glucose level is 66 mg/dL (3.66 mmol/L); no serum glucose is collected at the same time. A chest radiograph shows no focal consolidation.

Due to concern for sepsis, antibiotic drug therapy is initiated, but the patient's condition continues to deteriorate. He develops bruxism, ankle clonus, a positive Babinski reflex, and nystagmus. Magnetic resonance imaging of the brain with and without contrast does not reveal any abnormality. Electroencephalography shows diffuse cortical slowing without electrographic seizures or epileptiform discharges. Results of CSF polymerase chain reaction (PCR) for herpes simplex virus, enterovirus, West Nile virus, Epstein-Barr virus, cytomegalovirus, adenovirus, and varicella-zoster virus are negative. Bacterial CSF cultures and blood cultures are sterile. Additional laboratory testing reveals the diagnosis.

DISCUSSION

On hospital day 3, serologic testing for *Mycoplasma pneumoniae* immunoglobulin M was markedly elevated (1:2,889) using enzyme immunoassays. Throat PCR results were also positive for *M pneumoniae*. Levofloxacin therapy was initiated at that time, and his condition gradually improved. On hospital day 8, the patient was discharged with levofloxacin to complete a 7-day course. *Mycoplasma pneumoniae* CSF PCR results were negative and CSF cultures were sterile. Three days after discharge he was reexamined in the infectious disease clinic and was found to be back to his baseline and attending school with no restrictions.

The Condition

Encephalitis is the presence of inflammation in the brain parenchyma that is associated with clinical evidence of neurologic dysfunction. Acute encephalitis is a medical emergency with high morbidity and mortality. The clinical presentation includes fever, headache, nausea, vomiting, and altered mental status. *Mycoplasma pneumoniae* has been implicated as one of the commonest causes of encephalitis in children. In the California encephalitis project, *M pneumoniae* was observed to be the most common bacterial pathogen, accounting for 6% of all encephalitis cases. (1) Central nervous system (CNS) manifestations appear in 1 of 1,000 patients with associated *M pneumoniae* infections, (2) including encephalitis, meningitis, myelitis, polyradiculitis, Guillain-Barré syndrome, and peripheral and cranial neuropathy.

The most common presentation in children with *M pneumoniae*-associated CNS disease seems to be encephalitis or meningoencephalitis. In 13 children with *M pneumoniae*-associated neurologic sequelae, 10 presented with encephalitis or meningoencephalitis. (3) In a separate study of patients with *M pneumoniae*-associated CNS disease, 45 of 61 children had encephalitis. (2) Studies have shown *M pneumoniae* encephalitis occurring in pediatric patients of all ages. It remains one of the few treatable causes of encephalitis, but many physicians remain unaware of this, and *M pneumoniae* titers are still not part of the routine evaluation for encephalitis.

Diagnosis

Many patients with *M pneumoniae* encephalitis remain undiagnosed and untreated, thus prolonging morbidity. *Mycoplasma pneumoniae* encephalitis presents similarly to viral encephalitis. Co-infection with other viruses is common, and neuroimaging findings are usually normal. The electroencephalogram frequently shows diffuse slowing indicative of diffuse neuronal dysfunction.

Mycoplasma pneumoniae is difficult to isolate from CSF, and a negative result in CSF, either by PCR or culture, does not rule out the disease. (4) Because CSF studies are low yield, serologic studies of *M pneumoniae* immunoglobulin M or PCR specimens of throat swabs remain an important cornerstone in diagnosis. However, false-positives exist and can make interpretation difficult.

Pathophysiology

The pathogenesis of *M pneumoniae* encephalitis is thought to occur in 2 possible ways. The insult may occur either through direct bacterial invasion or through immunologic-mediated injury. If the prodrome is longer (≥ 7 days), the etiology is more likely to be immune mediated, whereas if the prodrome is less than 5 days, bacterial neuroinvasion is more likely. Furthermore, if the CSF culture grows *M pneumoniae*, the likely mechanism is through bacterial neuroinvasion. However, the pathogenesis for most cases is an immune-mediated injury due to antigenic similarities between *M pneumoniae* and brain tissue. Antibody-antigen complexes are formed and deposited within small venules in the CNS that causes neurologic injury.

Treatment/Prognosis

Antibiotic drug treatment has been suggested when the prodrome lasts less than 7 days because the likely pathogenesis is bacterial invasion. Case reports have shown improvement with treatment as well as complete neurologic recovery. However, the impact of antibiotic drug therapy has not been well studied. Because of their ability to cross the blood-brain barrier, quinolones or tetracyclines are preferred over macrolides. (4) Intravenous immunoglobulin was efficacious in 1 case when combined with antimicrobial treatment. (5) The prognosis for patients with *M pneumoniae* encephalitis is highly variable, with reports of long-term neurologic sequelae in 48% to 54% of patients with severe developmental delay, seizure disorder, and asymptomatic ventriculomegaly.

Lessons for the Clinician

- When presented with a case of encephalitis accompanied by respiratory symptoms or other extrapulmonary manifestations suggestive of *Mycoplasma pneumoniae* infection, early initiation of treatment with levofloxacin or doxycycline may be beneficial.
- Because the yield of cerebrospinal fluid *M pneumoniae* polymerase chain reaction and culture is low, including *M pneumoniae* titers as a standard test in the evaluation of encephalitis could be advantageous. (5)

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4 Chronic Dysphagia and Weight Loss in a 3-year-old Boy

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PRESENTATION

A 3-year-old boy presents to the emergency department with a 1-year history of dysphagia. Per his father, the boy has developed “strange eating habits” where he will place both juice and food into his mouth, swallow the liquid component, and spit out the solid components. Other associated symptoms include spitting up of saliva and progressive weight loss. There is no known history of throat pain, breathing problems, choking episodes, or witnessed foreign body ingestion. The boy has been previously seen by multiple pediatric providers, who attributed his spitting up, decreased oral intake, and weight loss to severe reflux, leading to repeated trials of antacid therapy without improvement in symptoms. Physical examination findings are normal except for the patient appearing malnourished and small for his age.

DISCUSSION

Differential Diagnosis

The differential diagnosis of a child presenting with gastrointestinal (GI) complaints such as dysphagia, recurrent emesis or spitting up, and weight loss is broad and includes gastroesophageal reflux disease, mechanical obstruction, migraine headaches, and food allergy, among other etiologies. A cause more commonly encountered in the acute setting but possible in the chronic setting is esophageal foreign body (EFB).

Actual Diagnosis

For this patient, the decision was made to proceed with an upper GI radiologic study, and a scout film revealed the presence of a radiopaque EFB that had the typical, circular shape of a coin but an unusual moth-eaten appearance (Fig 1). With this finding, a diagnosis of a chronic EFB after unwitnessed foreign body ingestion was made.

The Condition

Pediatric EFBs are exceedingly common. The American Association of Poison Control Centers reported more than 116,000 ingestions in 2000, and approximately 1,500 deaths per year in the United States are attributed to foreign body

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Figure 1. Scout film demonstrating a foreign body in the esophagus.

ingestion. This condition is largely associated with infants and young children, with 75% of these ingestions occurring in children aged 5 years or younger. This peaks during the ages of 6 months to 3 years. (1)(2) The most commonly ingested object by children in the United States is the coin, with 1 study reporting more than 250,000 coin ingestions and 20 deaths across 10 years. (1) This problem is so common, in fact, that it has been estimated that 4% of all children will at some point swallow a coin. (3)

Fortunately, the number of deaths from pediatric EFBs remains low. Most ingestions are witnessed or have clear symptoms of foreign body ingestion, allowing for early intervention. Many EFBs are also cleared spontaneously, including approximately 30% of ingested coins. (1) An estimated 40% of pediatric foreign body ingestions are unwitnessed, however, and up to half of all EFBs may not produce any symptoms. (2)

The symptoms of EFB are widely variable according to the object's shape and size as well as the patient's age. The likelihood of spontaneous clearance of a swallowed coin, for instance, decreases with coins larger than 23.5 mm (eg, a quarter) and in children younger than 5 years. (1) In addition, most EFBs are found at the thoracic inlet, indicating that foreign bodies that travel beyond this point are most likely to pass without incident. In a study by Dedhia, et al, (4) 72.2% of coins were found in the proximal esophagus, and coins in the distal esophagus were 9.3 times more likely to pass spontaneously than coins in the proximal esophagus. Symptoms of acute EFB include, but are not limited to,

blood in saliva; coughing; drooling; dysphagia or odynophagia; failure to thrive; fever; food refusal; foreign body sensation in the throat; gagging; irritability; pain in the neck, throat, or chest; recurrent aspiration pneumonia; respiratory distress; stridor; tachypnea or dyspnea; vomiting; and wheezing. (2) In a study by Little et al, (5) the most common presenting symptoms were dysphagia (37%), drooling (31%), and choking (17%). In a study by Sink et al, (6) the most common presenting symptoms were choking/gagging (49%), vomiting (47%), dysphagia and odynophagia (42%), cough (40%), and drooling (40%). Notably, the overlap in symptoms observed between these studies is minimal, and neither of these studies had consistent symptoms seen in more than half of the patients observed.

The presentation is further complicated by differences in symptoms seen with acute versus chronic EFBs. In a retrospective review by Miller et al, (3) 76% of patients with chronic EFBs presented with respiratory symptoms as the primary complaint, including respiratory distress, asthmatic symptoms, and cough. However, 22% of patients with chronic EFBs reported primarily GI symptoms such as nausea, vomiting, and dysphagia, and 1 patient in this study was asymptomatic. Both groups of patients (respiratory and GI complaints), though, had worsening of symptoms with meals. This variability was further seen in a study by Louie et al, (7) in which a history of wheezing and fever had the strongest association with unwitnessed EFB.

Local inflammation caused by chronic EFBs increases the risk of serious complications. Inflammation can progress to erosion and eventually complete perforation through the esophagus. Potential sequelae of esophageal erosion include stricture and diverticulum formation, which can result in dysphagia, food impaction, aspiration, recurrent pneumonia, and failure to thrive. Complete perforation can result in tracheoesophageal fistula formation, with a similar detriment to pulmonary health, and erosion to the adjacent aorta can lead to exsanguination and death. Even if the object passes through the esophagus there can be injury to esophageal mucosa. Sharp objects can lead to bowel obstruction, perforation, and erosion into adjacent organs.

The GI disorders related to a chronic EFB are also consistent with those that can lead to feeding disorders. According to a review by Manikam and Perman, (8) feeding disorders can occur in healthy children, children with GI disorders, and very commonly in children with developmental delays. Most feeding disorders have organic causes, but evidence has shown that many can be attributed to psychosocial factors and family dynamics. Even when the cause is organic, feeding disorders can be greatly improved

with treatment of the medical condition as well as behavior therapy to modify the child's learned feeding patterns and parent education.

Studies have shown that the risk of complications can be directly correlated with the duration of time that the object remains in the esophagus. A retrospective analysis by Denney et al (9) found that esophageal ulceration was seen with 15.5% of coins present in the esophagus for less than 12 hours, 22.6% of coins present 12 to 24 hours, and 45.5% of coins present for greater than 24 hours. These data support the need for early diagnosis and intervention by pediatric health-care providers.

Treatment/Management

The treatment for both acute and chronic EFBs is rigid or flexible esophagoscopy with removal of the foreign body under direct visualization. Once the patient has had the foreign body removed and has been stabilized surgically, management is largely supportive.

Patient Course

Otolaryngology was consulted and the child was taken to the operating room. Rigid esophagoscopy was performed, and the foreign body, consistent with a penny, was encountered in the mid esophagus, approximately at the location of the thoracic inlet. A forceps was used to grasp the penny, but the coin immediately fractured. The fracturing of the coin during removal and its moth-eaten appearance on plain film (Fig 1) were consistent with likely acid breakdown of the coin's metal alloy of copper and zinc. The fragment was removed, and the remainder of the coin was grasped and slowly worked free from surrounding granulation tissue involving the esophageal mucosa (Fig 2). After removal, the esophagoscope was advanced again to visualize the area. The presence of substantial erosion and granulation was verified, although complete perforation was not evident. To complete the procedure, a nasogastric tube was placed under direct visualization to allow for postoperative feeding access, bypassing the area of concern. Three days after surgery, a barium esophagram was performed, which revealed a contained perforation, or pseudodiverticulum.

The patient was discharged from the hospital on a liquid diet by mouth with enteral nutrition via a nasogastric tube for supplementation. Serial barium esophagram studies were performed during the next 3 months and showed ongoing severe reflux and unchanged pseudodiverticulum secondary to the chronic EFB. Due to concern by the treatment team that ongoing, uncontrolled reflux would impair healing and potentially lead to perforation, Nissen fundoplication and gastrostomy tube placement were performed. The pseudodiverticulum remained unchanged, and his clinical course



Figure 2. Photograph of a coin and a coin fragment after removal from the esophagus.

remained benign. He was started on feedings by mouth, which he tolerated, and 6 months after his foreign body was identified his gastrostomy was removed. Surgery to repair the diverticulum was no longer recommended given his stable diverticulum without symptoms.

Lessons for the Clinician

- Esophageal foreign bodies (EFBs) are common in the pediatric population and when promptly diagnosed and treated typically result in minimal morbidity and mortality.
- Typical EFB scenarios of witnessed ingestion, obvious choking, or complete food aversion do not always occur, as exemplified by this case of a child presenting with intermittent spitting up and chronic weight loss.
- Given the large variability in presentation of this condition and the severe complications associated with chronic EFBs, pediatricians and other pediatric health-care providers should maintain a high index of suspicion for foreign body ingestion when treating a young child with gastrointestinal or respiratory symptoms of unknown etiology and should consider imaging, such as a chest radiograph or even an upper gastrointestinal radiologic study, relatively early if symptoms persist despite treatment.

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Case 4: Chronic Dysphagia and Weight Loss in a 3-year-old Boy
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Index of Suspicion

4

Fever, Vomiting, and Abdominal Pain in a 23-month-old Girl

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PRESENTATION

A previously healthy 23-month-old girl presents to the emergency department with a 1-week history of fever (maximum temperature, 104.6°F [40.3°C]), vomiting, and abdominal pain. Vomiting occurs 3 to 4 times daily, and emesis is described as nonbloody and nonbilious. Her parents report that the patient has also been intermittently crying out in pain, clutching her belly. Associated symptoms include fussiness, decreased oral intake, and decreased urine output.

On initial physical examination the girl is sleeping. Her temperature is 98.6°F (37.0°C), heart rate is 137 beats/min, respiratory rate is 30 breaths/min, blood pressure is 104/69 mm Hg, and oxygen saturation is 100% on room air. She has dry lips, a mildly distended abdomen, and obvious facial grimacing (during sleep) with generalized light palpation of all 4 abdominal quadrants. Screening laboratory tests are significant for a white blood cell (WBC) count of 16,200/ μ L (16.2×10^9 /L) (50% neutrophils, 29% lymphocytes, 11% monocytes, 6% bands) and positive nitrites, positive WBC esterase, 10 to 25 WBCs, and bacteria on urinalysis.

An acute abdominal series (Fig 1) shows a "soft-tissue density in the right lower quadrant, likely stool-filled colon." Due to clinical suspicion for intussusception, abdominal ultrasonography (Fig 2) is performed, demonstrating a "nonperistalsing fecal ball-like structure in the right lower quadrant" but no target sign. Water-soluble contrast enema is performed, which shows no evidence of intussusception. Pediatric surgery determines no need for surgical intervention, and the patient is admitted by the pediatrics team for intravenous rehydration and treatment of possible pyelonephritis. Further evaluation reveals the correct diagnosis.

DISCUSSION

After admission, the patient continued to have abdominal pain, malaise, and fussiness. Of increasing concern was the persistence of abdominal distention and diffuse guarding on physical examination. Repeated abdominal ultrasonography was again inconclusive, so a CT scan of the abdomen/pelvis (Fig 3) was obtained for further evaluation of the appendix. CT revealed perforated appendicitis with a forming abscess and extravasation of contrast into the abscess, dilated loops of

AUTHOR DISCLOSURE Drs Keane and Whalen have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Acute abdominal series.

small bowel, and multiple air-fluid levels. The girl subsequently underwent laparoscopic appendectomy with surgical drainage of abdominal abscess. Pathology was consistent with gangrenous and perforated appendix. She received 1

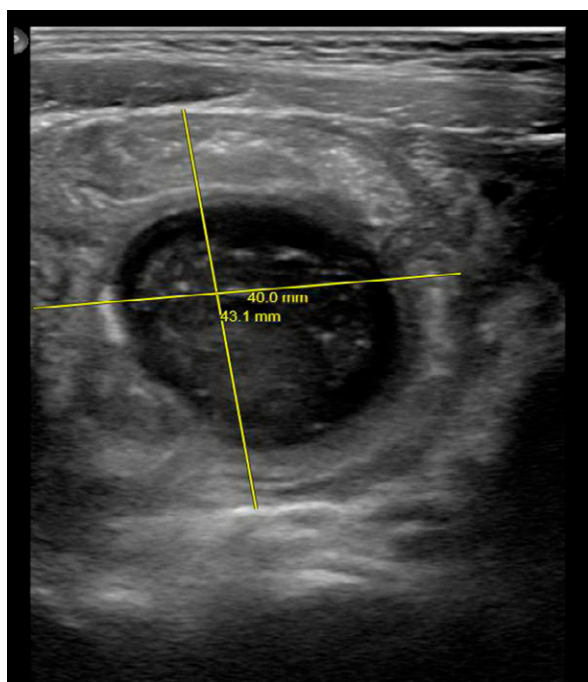


Figure 2. Abdominal ultrasonographic image, limited.

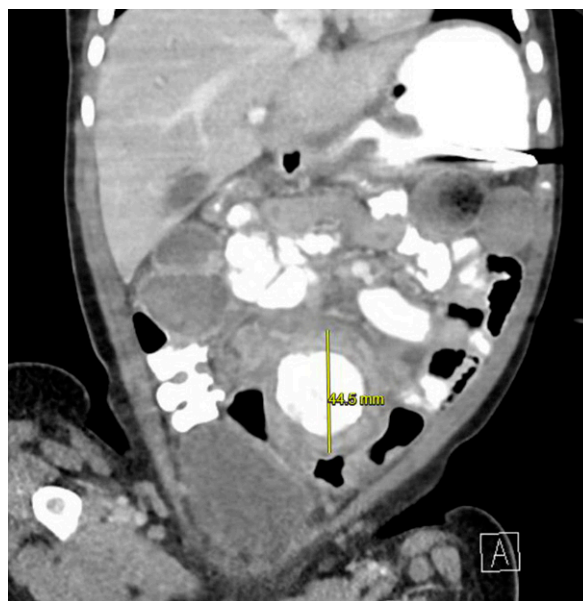


Figure 3. Computed tomographic scan of the abdomen/pelvis with contrast.

week of intravenous antibiotic drug therapy and was discharged on broad spectrum antibiotics. She fortunately experienced a full recovery.

This case highlights the importance of repeated physical examinations and the need for reevaluation when a patient does not improve as expected. Furthermore, it demonstrates the advantages of interdisciplinary cooperation and communication between medical teams. This patient was initially seen by pediatric surgery but was admitted by pediatrics and then cared for by both services. She underwent an extensive evaluation, including an arguably unnecessary water-soluble contrast study and inconclusive abdominal ultrasonography twice, before a CT scan was diagnostic.

The Condition

Appendicitis, although very common in the pediatric population as a whole, is rare in children younger than 2 years. In this young age group, the diagnosis of appendicitis is especially challenging because presentation differs and symptoms cannot be reliably described.

In the gastrointestinal tract, lymphatic tissue proliferation increases with increasing age and peaks in late adolescence. There is, therefore, a greater likelihood for appendiceal luminal obstruction and subsequent development of appendicitis in the teenage years. When infants and toddlers do get appendicitis, however, they are more likely to present with diffuse abdominal tenderness and peritonitis, not localized right lower quadrant tenderness as classically described.

In children younger than 2 years, there is frequently a delay in diagnosis, partially explained by the fact that young children lack the communication skills necessary to accurately describe their symptoms. Initial misdiagnosis rates are also very high. As was well-demonstrated in this case, appendicitis can be associated with pyuria and bacteriuria, leading to an incorrect diagnosis of urinary tract infection. In a young child with persistent abdominal pain and urinary signs of infection, appendicitis should, therefore, be considered. In general, appendicitis in this unique and vulnerable population is more likely to be complicated and is associated with increased morbidity.

Lessons for the Clinician

- In children younger than 2 years, appendicitis is associated with atypical presentation, delayed diagnosis, complications, and increased morbidity.
- Appendicitis can be associated with pyuria and bacteriuria, leading to an incorrect diagnosis of urinary tract infection.
- Appendicitis should be included in the differential diagnosis of a young child with persistent abdominal pain and urinary signs of infection.

Suggested Readings for this article are at <http://pedsinreview.aappublications.org/content/40/7/369>.

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4 Two Children with Presumed Inguinal Hernias

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CASE PRESENTATIONS

We present 2 patients, A and B, with a similar condition.

Patient A is a 7-year-old girl with no medical history who is referred to the emergency department by her pediatrician due to concern for incarcerated inguinal hernia. She has a 3-day history of genital area redness, pain, swelling, and dysuria. She has had similar, although less severe, episodes of inguinal area swelling without redness twice in the past year, which resolved spontaneously. She denies fevers, vomiting, or dyspnea. Her vital signs are normal. She does not have any breast development or pubic hair, with a sexual maturity rating (SMR) of 1. Her physical examination reveals bilateral labial redness, tenderness with swelling extending to the suprapubic and bilateral inguinal area, and an enlarged clitoris with no vaginal opening (Fig 1). Findings from a complete blood cell count, comprehensive metabolic panel, and urinalysis are unremarkable. Pelvic ultrasonography shows cellulitis of the labia minora without discrete fluid collection or abscess, testicles in the bilateral inguinal canals, and no definite uterus or ovaries.

Patient B is an 11-year-old girl with no medical history who presents to the emergency department with a 4-day history of abdominal pain, fever, nausea, and vomiting concerning for appendicitis. Her vital signs are normal. Her examination reveals right lower quadrant abdominal tenderness. She has SMR 2 breasts, SMR 1 pubic hair, and normal external female genitalia. Her pediatric appendicitis score is intermediate, and ultrasonography of her appendix is inconclusive. A follow-up computed tomographic scan of her abdomen and pelvis shows appendicitis but also reveals an absent uterus and gonadal tissue in the right hemipelvis as well as a soft tissue mass in the left inguinal canal that appears more like a testicle than an ovary (Fig 2).

DISCUSSION

The Condition

Androgen insensitivity syndrome (AIS), a disorder of sexual development, is a syndrome whereby a genotypically XY individual is phenotypically female due to a resistance to the androgen hormones through a mutation in the androgen receptor. There can be complete or partial resistance, as demonstrated in the

AUTHOR DISCLOSURE Drs Williams, Bruce, Patel, and Nesiama have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Physical examination findings for patient A.

cases presented. During embryotic development, the production of anti-Müllerian hormone (AMH) inhibits formation of the Müllerian ducts. These structures ultimately form the uterus, cervix, and proximal vagina. In AIS, AMH is present, but androgens secreted from the Leydig cells are not recognized and, therefore, no Wolffian ducts form to produce male genitalia. Because the innate tendency

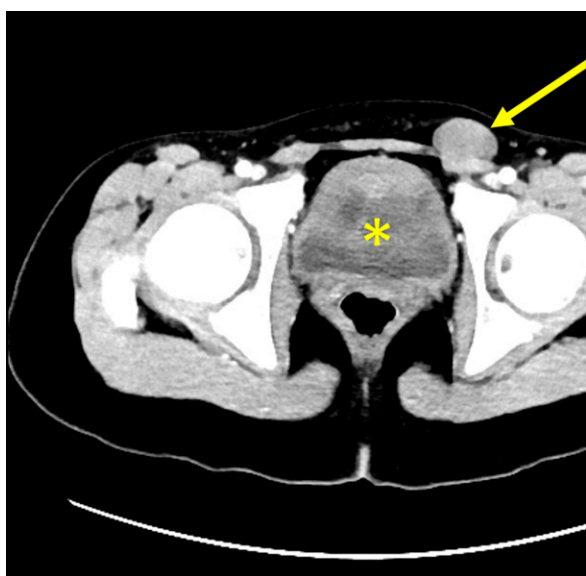


Figure 2. Computed tomographic scan of patient B with absent uterus (asterisk) and gonadal tissue in the left groin (arrow).

of human sexual development is female, the patient will develop external female genitalia. The syndrome may be first recognized with inguinal swelling in a phenotypic female, primary amenorrhea, or as a result of mismatch between prenatal sex prediction and the phenotype at birth. These patients go through puberty and develop estrogen through aromatization of the androgens. They enter puberty the same time as others and may be slightly taller, due to the growth-controlling region of the Y chromosome. There is a higher risk of gonadal tumors in AIS.

The pathogenesis of AIS is usually a missense mutation that encodes part of the androgen receptor. In complete AIS, the binding affinity is absent, whereas it is only altered in partial AIS. There are more than 800 mutations currently implicated in AIS. Whereas 30% of mutations are de novo, there is a X-linked inheritance pattern in complete AIS.

The differential diagnosis includes congenital adrenal hypoplasia, 5 α -reductase deficiency, and 3 β -hydroxysteroid dehydrogenase type 3.

Management

Management of AIS depends on the extent of the phenotype and should involve a multidisciplinary approach. Attention to various aspects, including functional, sexual, and psychological issues, should be undertaken. Furthermore, therapies such as gonadectomy, hormone replacement, and, in some cases, genitoplasty should also be discussed in accordance with the chosen sex and genetic advice.

Patient Courses

Patient A was given clindamycin for 10 days and was referred to the endocrinologist and gynecologist for further evaluation.

After extensive evaluation, she was diagnosed as having partial AIS. Her pertinent laboratory values include elevated testosterone of 126 ng/dL (4.4 nmol/L) (reference range, <10 ng/dL [<0.35 nmol/L]) and elevated AMH of 151 ng/mL (reference range, 0.53–7.78 ng/mL). The human chorionic gonadotropin stimulation test showed a normal testosterone to dihydrotestosterone ratio and a normal testosterone to androstenedione ratio. Fluorescence in situ hybridization and chromosomal microarray analysis showed 46, XY karyotype. No specific androgen receptor mutations were found on an androgen insensitivity panel. Of note, a physical examination revealing no vaginal opening in this patient during a previous visit to her pediatrician should have prompted earlier referral for evaluation.

She underwent a bilateral inguinal hernia repair, bilateral orchiectomy, and vaginostomy with vaginal calibration. A pathology specimen showed no evidence of Leydig cell hyperplasia. She will undergo induction of puberty at approximately 10 years of age and be raised as a girl.

Patient B was given metronidazole and ceftriaxone for her appendicitis. During the laparoscopic appendectomy, a testiculoform right gonad was found, and she had a left gonad measuring 2×3 cm that was fixed in the inguinal canal. She also had bilateral inguinal hernia. No uterus was identified. A vaginal examination was performed under anesthesia and revealed a vagina measuring 5 to 6 cm with no palpable cervix.

She was diagnosed as having complete AIS. Her pertinent laboratory findings included karyotype 46, XY and an elevated testosterone level of 136 ng/dL (4.7 nmol/L). The family also plans for her gonads to be removed with estrogen therapy during puberty. This patient will not need vaginal dilation given the initial measurements of her vagina. She will also be raised as a girl.

Lessons for the Clinician

- Always complete a thorough external genital examination in any child with lower abdominal pain or inguinal area swelling.
- Androgen insensitivity syndrome (AIS) should be included in the differential diagnosis for a girl with inguinal area swelling or primary amenorrhea.
- Management of AIS should be undertaken by a multidisciplinary team.
- Gonadectomy is recommended because of the small risk of gonadal tumors.

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